Antioxidant therapy for severe sepsis: Promise and perspective*

Human sepsis reflects a complex systemic process in which alterations occur in every metabolic and regulatory system that has been studied (1). Clinical data demonstrate activation of the host's inflammatory and anti-inflammatory pathways in a near simultaneous event (2), with increased necrosis and apoptosis of circulating immune effector cells (3, 4), immune suppression (5, 6), inducible nitric oxide synthase activation with associated vasodilation (7), adrenergic receptor down-regulation (8), insulin resistance (9), microcirculatory disturbances (10), organ-system dysfunction (11), changes in hepatic synthetic preference (12), and in some cases mitochondrial dysfunction (4, 13, 14). When interfaced with genetic differences in host responsiveness and resiliency and premorbid status of each subject, it is amazing that any consistent pathophysiologic process can be identified or treatment universally useful (15). The failure over the past 10 yrs of numerous immunomodulating therapy clinical trials in the management of patients with severe sepsis that targeted single point inhibition or augmentation of specific key processes in the expression of sepsis only underscores this reality. For example, no benefit was seen when anti-tumor necrosis factor antibodies, interleukin-1 receptor antagonists, supra-physiologic oxygen delivery, and nitric oxide synthase inhibition were studied in sepsis shock patients. Potentially, these treatments act too distally to the initiating or propagating process, only hide a symptom unrelated to cure, or are applied too late in the process of the host's response to stress to have a positive effect on outcome. The one immunomodulating treatment shown to be effective in the management of patients with severe sepsis, namely activated protein C, worked even in patients whose baseline serum protein C levels were normal (16). Thus, we still do not know the reason why that study demonstrated a good outcome.

Central to the initial activation of the innate immune response and the systemic injury associated with the subsequent systemic response is oxidative stress, both as an intracellular signal and an extracellular effect. Polymorphonuclear leukocytes excrete large quantities of oxygen free radicals and nitric oxide in response to exposure to foreign substances (17). These substances induce cellular injury in target tissues by damaging lipid membranes, intracellular metabolic machinery, and DNA structure through production of hypochloric acid, superoxide, hydrogen peroxide, and peroxynitrate (18–20). Importantly, oxygen free radicals and other intracellular oxidant small molecules (e.g., peroxynitrate) are the primary intracellular "second messengers" in the intracellular signal transduction of the inflammatory response from cell surface receptor activation to gene transcription (1). Oxidative stress-responsive mediators include both proinflammatory promoter factors, such as nuclear factor (NF)-κB, and anti-inflammatory promoter factors, such as heat shock factor-1. Both NF-κB and heat shock factor-1 migrate to the nucleus, where they selectively augment gene transcription for specific functional proteins. If intracellular oxidative stress were to be reduced, then both anti-inflammatory and proinflammatory gene transcription may be inhibited.

Numerous antioxidant compounds are present at rest in naïve cells, in extracellular fluids, and in the circulation, and their expression is markedly up-regulated in response to stress, suggesting that antioxidant species reflect an intrinsic host-defense mechanism. One of the main scavenger systems for cleavage of free radicals is the selenium-dependent glutathione peroxidase (20). Patients with sepsis tend to have low plasma concentrations of selenium, and in one small randomized controlled trial in patients with sepsis, Angstwurm et al. (21) demonstrated that selenium replacement reduced organ dysfunction and improved clinical outcome. Furthermore, overexpression of antioxidant compounds using gene transfer techniques and simple infusions of antioxidants reduces mortality rates and organ injury in animal models of sepsis (22). N-acetylcysteine (NAC) is such an antioxidant that replenishes glutathione stores. NAC has been shown to inhibit NF-κB activation in tissue culture and animal models of sepsis. NAC has the potential advantage of being readily available, nontoxic, and relatively inexpensive. Thus, if NAC infusions were shown to improve outcome of sepsis patients, then this would reflect a very important positive development.

In this issue of *Critical Care Medicine*, Dr. Paterson and colleagues (23) document for the first time that NAC infusions in patients with severe sepsis inhibit *in vivo* NF-κB activation in circulating blood mononuclear cells. They also demonstrate that interleukin-8, a potential polymorphonuclear leukocyte activating substance, was also selectively reduced following NAC treatment, whereas neither of these effects occurred in the control subjects. These data suggest that NAC reduced the systemic proinflammatory state. Finally interleukin-6, a nonspecific marker of inflammation, was reduced in all subjects, whereas soluble intracellular adhesion molecule-1, a marker of circulating immune cell activation, remained elevated in all subjects. These data reflect a "proof of principal," that NAC can inhibit NF-κB activation in human sepsis. The authors also performed an *in vitro* study using isolated human peripheral blood mononuclear cells from normal volunteers. They documented that very high levels of NAC in the culture media (>25 mmol/L) could block NF-κB activation in response to lipopolysaccharide exposure. These *in vitro* data, however, are of questionable clinical significance because the NAC levels needed to induce this inhibition in this model were well above those attainable *in vivo*. Still, this report places NAC firmly in the area of potential clinical treatments whose preliminary clinical studies suggest a measurable immunologic effect.

*See also p. 2574.

Key Words: antioxidants; sepsis

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Potentially, NAC could be beneficial to the patient with sepsis for a variety of reasons. Oxidant-induced endothelial damage occurs when activated white blood cells bind to the vascular endothelium (19). Since antioxidant capacity is reduced in sepsis (18), increased circulating antioxidant capacity may minimize this cytotoxicity. Second, if NF-κB is inhibited, it should also minimize the downstream proinflammatory and vasodilatory actions of sepsis (24). Thus, downstream deleterious clinical effects of sepsis may be minimized. Third, since nonsurvivors of severe sepsis display an up-regulation of both NF-κB and HSP-1 nuclear binding, whereas survivors display a markedly reduced nuclear binding of both oxidant-induced promoters, relative to normal controls (5), if NAC reduced overall oxidant-induced promoter nuclear binding, it would create a cellular genetic expression that resembles survivors from severe sepsis.

Although these data look exciting, there is much need for caution and deliberation about the use of NAC in septic patients, even before going forward with any large-scale clinical trial. First, on a purely mechanistic level, it is not clear that blunting the host inflammatory response is a good thing to do. Immune suppression, rather than immune activation, characterizes severe sepsis (6). Patients die of nosocomial infection despite being on potent broad-spectrum antibiotics. Second, creating a genetic phenotype similar to survivors does not mean that survival rates will improve in treated septic patients. Recall that nonspecific nitric oxide synthase inhibition, although reversing nitric oxide-induced pathologic vasodilation in patients with severe sepsis, also resulted in increased mortality rates in the treatment group despite normalization of system blood pressure (25). In that study, nitric oxide synthase inhibition reduced cardiac output and oxygen delivery, presumably because of the associated increased left ventricular afterload. Furthermore, augmenting cardiac output to survivor levels in severely ill patients only increased mortality rate over controls (26). Thus, resembling characteristics of survivors from severe sepsis without addressing the primary cause of the process may not be a good therapeutic strategy.

We have come a long way in understanding the processes that induce and sustain the septic response in our critically ill patients. New clinical studies are being published monthly documenting improve survivorship of septic subjects treated aggressively with traditional therapies but applied in a closer titrated fashion (9, 17). As with these new modifications of traditional treatment, NAC has the advantage of addressing a fundamental aspect of the inflammatory response and, as such, is an agent with promise in the treatment of severe sepsis. I hope future clinical trials of NAC in patients with severe sepsis will reflect a thoughtful, metered approach using both proven traditional cardiopulmonary management and immunomodulating therapies and that these trials will be powered to show benefit even in specific patient subsets in whom selective antioxidant therapy would induce the greatest benefit.

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Determination of infection probability versus the diagnosis and treatment of antibiotic-responsive diseases*

Soap and water and common sense are the best disinfectants—Sir William Osler (1)

A nidus of infection leads to sepsis, followed by adverse and intractable immune consequences and then death in some patients. Detect and eradicate infection early in its clinical course, and you resist the odds of patient demise in the intensive care unit (ICU). The eternal problem is divining the presence of infection; what is the acceptable burden of proof that a critically ill patient is actually "infected"? Missed infection can lead to sepsis and all of its penalties. So too, unwarranted treatment of "noninfections" directly and indirectly causes morbidity in many patients and mortality in some patients.

The criteria for determining the presence of infection have been described and quantitated by numerous authors and researchers (2–6). The Centers for Disease Control (CDC) published standardized definitions and criteria for nosocomial infections in 1988 (2). The purpose of these criteria is to standardize data collection regarding the presence or absence of nosocomial infections in a given patient. More simplistically, standardization is in place to differentiate one hospital's pneumonia from another hospital's bronchial colonization. The National Nosocomial Infections Surveillance System is wholly dependent on the consistent application of these CDC criteria and data collection across hospitals.

A by-product of the CDC definitions of nosocomial infections has been their clinical application for patient management. These criteria have been applied to measure and enhance the precision of nosocomial infection diagnoses in many ICU settings. Unfortunately, these objective criteria are not always objectively applied by individual practitioners in the ICU. As a result, antibiotic misuse and improper diagnosis of ICU nosocomial infections remain significant and intractable problems.

In this issue, Dr. Bota and colleagues (7) introduce a metric to determine the probability of infection in critically ill patients. Using the CDC criteria as a benchmark (to define the presence or absence of infection), the authors developed and validated a scoring system based on heart rate, respiratory rate, temperature, C-reactive protein, and the Sequential Organ Failure Assessment score in their patient population. The Infection Probability Score (IPS) yields a numerical value that is statistically correlated with the presence or absence of infection. At an IPS of 14 (selected cutoff score), the positive predictive value was 53.6% and the negative predictive value was 89.5%. That is, the probability that an infection is present in a patient with an IPS >14 is 53.6%, and it is 10.5% in a patient is with an IPS <14. The most common confounding, noninfectious medical problems at a score >14 were cerebral events and pancreatitis.

The sensitivity and specificity of a diagnostic test in predicting the presence or absence of a target condition vary with the choice of threshold. Choosing this threshold is a subjective determination that is based on science but also patient care philosophy. To determine the single best discriminator between the presence or absence of infection, Dr. Bota and colleagues (7) constructed receiver operating characteristic curves and chose a threshold value at which the sum of sensitivity and specificity reached a maximum (IPS = 14). However, this approach can be insensitive to the relative penalties of misclassifying patients.

We should ask whether the relative risk of withholding antibiotics from 10% of patients with an infection (IPS <14) is comparable to the risk of initiating antibiotic treatment in 46% of patients without an infection (IPS>14). The literature on ICU-acquired pneumonia, the most common nosocomial infection in the ICU, underscores this uncertainty (reviewed in Ref. 8). The attributable mortality rate from nosocomial pneumonia is as high as 3.6%. Several observational studies have shown that the immediate initiation of appropriate antibiotic therapy is associated with reduced mortality rates in patients with pneumonia (9, 10). At the same time, there is evidence suggesting that observed excess mortality rates associated with inappropriate (or delayed) antibiotic administration are not reduced by later correction of these regimens (when culture results become available) (11). Thus, it is imperative to initiate appropriate antibiotics as soon as a patient exceeds the threshold for the suspected presence of pneumonia.

Unfortunately, there is also a penalty for prescribing antibiotics to patients who are not infected. Prior antibiotic use is a major risk factor for the development of nosocomial pneumonia, with an estimated odds ratio of 13 (12). Many ICU practitioners may be uncomfortable with the care philosophy of not treating 10% of patients with an infection, as the selected IPS threshold of 14 could be interpreted.

The IPS is an effort to simplify the determination of the presence of infection into a bedside tool that will modify physician behavior. A high IPS is a reminder to the care provider to search for an infection, whereas a low IPS suggests the need to reevaluate the indications for a prescribed antibiotic. The authors are to be lauded for their efforts to develop such an index. However, as with other scoring system indexes, the role of the IPS is to supplement clinical judgment (by establishing the pretest probability of additional diagnostic tests, such as microbial cultures).

***See also p. 2579.**

Key Words: infection probability score; nosocomial infection; pneumonia; receiver operating characteristic curve; epidemiology of infection

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The best diagnostic methodologies and therapeutic interventions are only effective if they are actually adopted and used by clinicians. Guyatt et al. (13) have editorialized that continuing education has little effect on modifying physician behavior. Habit, local practice patterns, and product marketing seem to be more powerful determinants of physician behavior. The authors additionally comment that methodologies that do not require knowledge of original medical literature, and instead focus on behavior change, also may be effective modifiers. What we should glean from this is that any tools we develop, not just to detect infection but to guide the appropriate therapeutic response, must be seamlessly integrated with existing care processes. To do less ensures that our current system of diagnosing and treating infection in the ICU, with its attendant shortfalls, will not change.

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Proposed mechanism for induction of heat shock protein 70 by geranylgeranyl acetone by prenylation of Ras proteins*

In this issue of *Critical Care Medicine*, Dr. Massuda and colleagues (1) demonstrate the protective effect of geranylgeranylacetone (GGA), an anti-ulcer drug widely used in Japan, by induction of heat shock protein (HSP) 70 in the rat diaphragm of a cecal ligation and perforation (CLP) sepsis model. They demonstrate an association between GGA and up-regulation of HSP70 expression; however, the molecular mechanism by which this up-regulation occurs remains unknown. Geranylgeranylation of Ras proteins by GGA might be responsible for this up-regulation of HSP70 via increased activation of Ras pathways.

*See also p. 2585.

Key Words: geranylgeranyl acetone; prenylation; Ras; heat shock protein 70; geranyl; farnesyl

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Prenylation is the process of enzymatic posttranslational lipidation of proteins. This process involves the formation of thioesters by the addition of either farnesyl (15 carbons) or geranylgeranyl (20 carbons) isoprenoids to cysteine residues at or near the C terminus of proteins.

The majority of prenylated proteins, particularly of the Ras superfamily, have a conserved C terminal motif CaaX, whereas C is cysteine, a is aliphatic, and X is any carboxy terminal amino acid (2). The process of prenylation is specifically mediated by farnesyl or geranylgeranyl transferases. It was noted that if X is leucine, then the nearby cysteine will undergo geranylgeranylation (as opposed to farnesylation) (3). Specific endoproteases cleave the last three amino acids of the prenylated CaaX box, which is followed by carboxyl methylation of the cysteine residue. The result is an increased lipophilic nature of the prenylated, methylated domain of the protein (4).

Prenylation of the Ras superfamily of proteins is of particular interest. The Ras superfamily of proteins includes a large group of signal transduction regulatory proteins. Included are RAS, Rho/Rac, Rab, Arf, and Ran families of proteins. These proteins are classified as small guanosine 5'-triphosphatases due to their guanosine 5'-triphosphate/guanosine 5'-diphosphate binding properties and small monomeric structure. Because of their hydrophilic nature, their targeting and association with the cellular membrane are made possible by lipid modification (prenylation) and methylation. These processes afford the localization/anchoring of these G proteins to the inner cellular membrane where they exert their signaling regulatory role and possibly facilitate their protein-protein interactions.

It appears that prenylation of Ras proteins is important for their interaction

with guanosine 5'-triphosphatase activating proteins and subsequently for regulating Rac signaling mechanisms (5). The G proteins of the Rho/Ras family are central players in the regulation of stress-inducible signal pathways involved in cell death and survival.

Induction/activation of heat shock genes in response to cellular stresses such as heat, genotoxins, heavy metals, and hypoxia-reperfusion is transcriptionally mediated by heat shock factors (6). Reactive oxygen species also have been implicated to activate heat shock factors (7–9).

PI3 kinase, JNK, and nuclear factor-κB are all associated with the induction of heat shock factors and HSP (10, 11). It is conceivable that prenylation of Ras proteins and their subsequent localization to the cell membrane, particularly in sepsis, where transmembranal G protein is signaled by various stimuli, including Ca^{2+}, nitric oxide, diacyl glycerol, growth factors, and others, activate Ras pathways that lead to increased transcription of HSPs.

If indeed GGA increases geranylgeranylation of Ras proteins and their localization to the cellular membrane, followed by the activation of Ras pathways (such as in sepsis), then caution is in order. The activation of oncogenic mutations of the Ras gene is common in cancer, and inhibition of farnesyl transferases is a strategic target for anticancer therapies of cell signaling both in Ras transformed cells and in cancers without oncogenic Ras mutations (12).

Future research should investigate the influence of GGA on Ras cellular localization and subsequent protein expression as a result of various G protein receptor signaling associated with sepsis. The potential oncogenic effects of GGA on Ras activated cells also should be explored.

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Are recruiting maneuvers needed when ventilating acute respiratory distress syndrome?*

The rationale favoring lung recruitment in the ventilatory management of acute respiratory distress syndrome (ARDS) has been established by an experimental and observational database of impressive scope and consistency (1, 2). Apart from improving gas exchange, sustained recruitment is believed important in avoiding ventilator-induced lung injury (VILI). Although considerable emphasis has been placed on the need to recruit so as to avoid tidal opening and reclosure of unstable lung units, such dynamics clearly are not the only mechanism at work in the genesis of VILI. The tensions developed at the boundaries of aerated and nonaerated tissues substantially exceed those in fully open regions (3). When the lung is repeatedly subjected to high inflating pressures, these "boundary" stresses may give rise to damaging shearing forces, vascular stress fractures, or sufficient distortion of the cytoskeleton to incite inflammation (1, 2, 4). Methods to "open" the lung without raising peak tidal pressure (recruiting maneuvers, RMs) are therefore of potential value—a principle that has been reinforced by evidence from surfactant washout models of acute lung injury and from selected clinical settings, such as high-frequency oscillation (5). An article by Dr. Brower and colleagues (6) from the ARDS Clinical Trials Network (ARDSnet) that appears in this issue of *Critical Care Medicine* indicates that RMs are often ineffective, limiting their worth at the bedside. These disappointing data remind us that the value of RMs is highly conditional on the specific circumstances under which they are undertaken.

In the mechanically heterogeneous environment of the acutely injured lung, "high-risk" junctional interfaces are pervasive but tend to predominate in gravitationally dependent zones (7, 8). Infiltrated alveoli deep within diseased regions are remote from the air space and therefore unlikely to be exposed to amplified forces of expansion. Furthermore, many lung units that are juxtaposed to aerated regions are consolidated, rather than collapsed or partially flooded, and consequently cannot be "opened" under

*See also p. 2592.

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any circumstances. Some of these expansion-refractory alveoli coexist alongside potentially inflatable ("recruitable") but unstable units that collapse or gas trap at some positive value of airway pressure. The percentage of lung units that are unstable is relatively small, especially in the later stages of disease (8). Yet, because recruitment occurs along the entire inspiratory limb of the pressure-volume envelope, some unstable lung units may open and close with each tidal cycle, whatever choices for positive end-expiratory pressure (PEEP) and tidal volume are made (9). Those that open at high pressure are most vulnerable to damage.

Fortunately, the majority of unstable lung units can be kept open by airway pressures that are in a much lower range than the pressures needed to open them (8, 10). Conceptually, therefore, the periodic application of sustained high pressure—a "recruiting maneuver"—might pry open lung units that can remain patent at well-tolerated levels of PEEP and thereby reduce the quantity of lung subjected to "stress focusing" and VILI when relatively high tidal inflation pressures are used (10, 11). But a key question relates to how long these newly RM-opened units stay open after PEEP and tidal volume return to their original values. Using pulse oximetry as a practical—if insensitive and often inaccurate—marker of RM response, the ARDSnet group found only very modest and short-lived benefits after briefly applying a sustained pressure similar to that which corresponds to the total lung capacity of normal subjects (6). Why not?

Considering what is now understood about ARDS mechanics and pathoanatomy, these unimpressive results are neither unexpected nor difficult to reconcile with prevailing theory. Recruiting response is a joint function of the number of unstable units (the potential for recruitment), the pressures needed to open them, the aggressiveness of the maneuver applied, and the tolerance of the patient to such interventions. Patients with secondary (extrapulmonary) lung injury who are ventilated with low levels of PEEP and do not reach high plateau pressures during tidal breathing are those most likely to have "recruitable" atelectatic or partially flooded lung units—especially in the earliest stages of their illness (12). On the other hand, patients with primary (pulmonary) forms of ARDS often require pressures exceeding 50–60 cm H_2O to open refractory units. Even in patients with primary disease, however, most lung units are kept from collapsing by PEEP levels <15 cm H_2O (8). Those lung units that require high pressures to open are generally the first to close when pressure is reduced. Moreover, the dynamics that initially led to alveolar instability are quickly reestablished as tidal cycling resumes. Sustained response to a recruiting maneuver performed in the supine position, therefore, should not be expected if neither the PEEP level nor the tidal plateau pressure changes afterward. Conversely, higher PEEP will help keep open some of the units opened during the RM.

Even though traditionally used, widely employed, and selected for most previous research studies (including this one), the application of sustained high pressure (high-level continuous positive airway pressure) is no more effective as an RM and tends to be less well tolerated hemodynamically than recruiting methods achieving lower average pressures but similar peak pressure during the inspiratory phase of pressure controlled ventilation (13). With the possible exception of prone positioning, all recruiting maneuvers temporarily alter the cardiac loading conditions and therefore may influence hemodynamics. As airway pressure increases, the back-pressure for venous return is increased, often reducing right and/or left ventricular preload. Simultaneously, recruitment-associated lung expansion may result in either increased pulmonary vascular resistance or, when the recruitment of capillary bed and release of hypoxic vasoconstriction predominate, in unchanging or even reduced right ventricular afterload.

The ARDSnet results must be interpreted with these factors in mind. Starting from relatively high levels of PEEP and plateau pressure, returning to those same values post-RM, and using the traditional sustained inflation method with a recruiting airway pressure designed more to ensure safety than effectiveness, typical recruiting effects in the current study were ineffective and short lived. Moreover, fully two thirds of patients had pneumonia or aspiration as the underlying cause. In the ARDSnet experience, barotrauma was not a problem, and very few patients experienced adverse hemodynamic effects, as judged by blood pressure and heart rate responses (6). The latter results conflict with those of Grasso et al. (14), who in a more comprehensively monitored patient sample found an inverse correlation between hemodynamic compromise and lasting gas exchange response when using a similar but somewhat more aggressive "sustained inflation" type recruiting maneuver.

Dr. Brower and colleagues (6) address the important limitations and shortcomings of this study in the well-balanced self-critique they provide. Other recruiting methods, other types of patient, other initial conditions, and other choices for recruitment assessment and post-RM management are likely to have justified different conclusions. Their reticence to endorse RMs on the basis of these results is also reasonable; performing scheduled RMs routinely without subsequently altering PEEP or tidal volume when oxygenation improves does not seem rational. Yet, although much more work needs to be done to clarify some points of uncertainty, RMs have become an entrenched part of my own practice, as an RM clarifies the extent to which benefit can be expected from higher levels of PEEP and defines the patient's sensitivity to alterations of the heart's loading conditions. Moreover, because it now seems sensible to titrate PEEP "from above downward" along the deflation limb of the PV curve to the lowest tolerated level (15), RMs are an inherent part of this empirical process.

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Still unresolved issues with brain-type natriuretic peptide measurement in the critically ill patient*

Brain-type natriuretic peptide (BNP) is a regulatory protein that has the potential to indicate chronic hemodynamic stress as well as acute fluid or pressure overload to the ventricles (1). Natriuretic peptides like BNP or NT-proBNP are currently being used as diagnostic and prognostic markers in congestive heart failure and acute coronary syndromes and are helpful for monitoring therapy in decompensated heart failure (2–4).

In this issue of *Critical Care Medicine*, Dr. McLean and colleagues (5) provide valuable data on the usefulness of BNP to predict cardiac dysfunction in critically ill patients. This particular patient population has a high prevalence of cardiac dysfunction. However, in these patients, advanced age and the presence of renal failure, lung disease, pulmonary embolism, acute coronary syndromes, and diseases with high natriuretic peptide output like liver cirrhosis represent potential confounders and have to be considered in the interpretation of BNP results (6).

The present article focuses on the effects of age, gender, and renal function on BNP concentrations in these patients. The study consistently confirms the predictive value of BNP in patients requiring intensive care (7). However, the results question the application of a single cutoff level and rather favor different cut-points for males and females stratified for age. In this article, age and gender accounted for 30% of the variation in BNP levels in this specific patient population.

This is a very interesting finding since previous reports suggested that BNP concentrations are less influenced by age, gender, or renal function than NT-proBNP concentrations (8). Accordingly, a single FDA approved cut-point for the diagnosis of congestive heart failure has been established for BNP (7, 9). In contrast, age- and gender-dependent cut-points are being recommended for NT-proBNP. In addition, the present study suggests a relationship between BNP and renal function that may be important in specific study populations like emergency cases or in patients with chronic or critical disease.

The exact reason why age and gender affect natriuretic peptide concentrations remains unclear. The hypothesis that the prevalence of cardiac dysfunction increases with age and may be responsible for higher BNP concentrations in older patients has been questioned recently (10). The present data rather suggest an independent effect of age that is unrelated to cardiac abnormality

Chronic kidney disease previously has been reported to influence the optimum cut-points for BNP in the diagnosis of congestive heart failure. McCullough et al. (11) suggested a higher cut-point of approximately 200 pg/mL for patients with a markedly reduced glomerular filtration rate.

The overt discrepancy between NT-proBNP and BNP with respect to different cut-point recommendations and results, however, is difficult to explain since BNP is cleaved from NT-proBNP and should be present in equimolar concentrations in blood.

There are several possible mechanisms that may explain this discrepancy. First, patients with renal failure frequently have been excluded from trials supporting a single cut-point of 100 ng/mL (7, 9). In addition, there is not uniform adherence to the Food and Drug Administration approved cut-point as other investigators established and proved the usefulness of lower and higher cut-points (2, 12). In addition, some preanalytical and analytical findings may explain some variance of BNP measurements (13, 14). First, BNP is less stable than NT-proBNP when stored at room temperature. In addition, some BNP may escape detection due to proteolytic degradation in blood or binding to clearance receptors, whereas NT-proBNP remains intact until renal clearance. Moreover, the half-life of NT-proBNP is 120 mins, resulting in higher cumulative blood concentrations in patients with cardiac disease than with BNP, which has a half-life of 22 mins and should allow more subtle identification of acute changes.

***See also p. 2611.**

Key Words: brain-type natriuretic peptide; age; gender; renal function; cutpoints

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Finally, BNP is measured with a whole blood point-of-care test that has an imprecision between 9% and 15% (9). Recently, automated immunoluminometric assays for NT-proBNP and BNP with substantially lower intra- and interassay imprecision of <6% have been introduced (15).

Whether biochemical or analytical differences between BNP and NT-proBNP have a clinical relevance is largely unsettled. Current evidence, however, suggest comparable diagnostic and predictive values for BNP and NT-proBNP in most clinical applications (16).

The present study suggests that application of one cut-point for BNP may not be adequate to diagnose cardiac dysfunction in critically ill patients. In these patients, different cut-points for males and females stratified for age may be warranted for optimal results with BNP measurements.

In addition, the study highlights some issues with BNP that have not been adequately addressed so far, such as sample stability, assay precision, and interference with heparin or other drugs. These issues are gaining importance with introduction of automated immunoluminometric assays for both NT-proBNP and BNP and will require objective head-to-head comparison of clinical significance in forthcoming studies.

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Ventilators: How clever, how complex?*

The first positive pressure ventilators were simple mechanical devices that moved gas into an endotracheal tube (ETT) and allowed passive exhalation. These first gas pressure driven ventilators were followed by the electromechanical devices that dominated the scene from the late 1960s until the mid-1980s. The development of electromechanical ventilators allowed introduction of the concept of partial ventilatory support with intermittent mandatory ventilation. With the advent of intermittent mandatory ventilation, the patient now was asked to breathe through the ventilator circuit; work of breathing imposed by the ventilator became of paramount importance. When the personal computer burst into the world of medical technology in the 1980s, it was rapidly adapted to control the gas flow generator that is at the heart of modern ventilators. Gas flow that previously had been modulated with mechanical bellows and valves now could be controlled by software that could rapidly alter patterns of pressure and flow. The control of gas flow is now limited only by the imagination of the engineers and clinicians who design ventilators.

*See also p. 2619.

Key Words: positive pressure ventilators; endotracheal tube; electromechanical ventilators; ventilatory support; intermittent mandatory ventilation

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Before the introduction of the microprocessor-controlled ventilators, the only form of partial ventilatory support was intermittent mandatory ventilation. The new ventilators allowed additional modes of partial support such as pressure support ventilation (PSV), which augments inspiratory flow during a patient-initiated breath and has become a widely used mode during weaning. Unlike PSV, which augments gas delivery to the patient, automatic tube compensation (ATC) increases the pressure assist to compensate for the pressure decrease across the ETT. During inspiration, the pressure assist is increased; during expiration, the airway pressure at the proximal end of the ETT is lowered. The intent of ATC is to compensate for the tube-imposed increase in work of breathing.

In this issue of *Critical Care Medicine*, Dr. Elsasser and colleagues (1) have compared ATC systems in three commercially available ventilators and a prototype ATC system devised by their group. They compared the performance of these ATC systems using a test lung fitted with ETTs of varying sizes at four levels of positive end-expiratory pressure and two ventilatory rates. They concluded that ATC decreased tube-related inspiratory but not expiratory work of breathing. In other articles, the authors and their collaborators have demonstrated that ATC systems are more comfortable in volunteers (2) and compensate for tube resistance in tracheally intubated patients (3). Despite efficacy in overcoming tube resistance, demonstrations of improved patient outcomes are lacking. Haberthur et al. (4) did not observe significant differences between pressure support and ATC during the final phase of weaning, although they suggested that a successful breathing trial with only ATC might better predict successful extubation. Oczenski et al. (5) also failed to detect any difference in outcome with ATC compared with PSV using an oxygen consumption based methodology to detect work of breathing.

Since ATC is designed to overcome tube resistance only, one of the potential risks of the technique is overassist, that is, ventilating the patient. Although the test lung model used in this study demonstrated that overassist did not occur in the laboratory setting, it is possible that in clinical use this could happen. The algorithms used to estimate ETT resistance are based on a measurement of airway pressure at the proximal end of the tube. Banner et al. (6) showed that the most accurate measurement of both work of breathing and ETT resistance is best determined by measuring tracheal pressure at the distal end of the ETT. Hotchkiss et al. (7) demonstrated with mathematical modeling that unstable behavior characterized by oscillations in tidal volumes and end-expiratory pressure could occur with PSV under clinically realistic conditions of air flow obstruction. In other words, the response of the patient-ventilator unit may not be predicted by test lung conditions.

Because the complexity of the air flows in the patient on a mechanical ventilator are not adequately modeled under test lung conditions, the clinical response to a modality such as ATC may vary. Eliminating ETT-imposed work of breathing is desirable during the latter phase of weaning, and ATC may prove useful in achieving that goal. This and other technical improvements in the software that controls gas flow in the modern ventilator must be integrated into a diligent and attentive plan of patient care.

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Carbon dioxide: A "waste product" with potential therapeutic utilities in critical care*

Whereas CO_2 is the essential building block for all products in the plant kingdom, it has been considered a "waste product" in the animal kingdom (1), despite its major role in acid-base homeostasis, control mechanisms of breathing, and chemical regulation of cerebral blood flow. Recent studies suggest a potential utility for CO_2 in pulmonary critical care, termed therapeutic hypercapnia (TH) (1–4). In the current issue of *Critical Care Medicine*, Dr. Laffey and colleagues (4), in a prospective, interventional, randomized study, provide a new approach supporting the importance of hypercapnia in reducing ventilator-induced lung injury. TH is a type of permissive hypercapnia in which CO_2 is deliberately added to inspired gases to elevate $Paco_2$. Permissive hypercapnia, with controlled ventilation, already has become a clinically acceptable ventilation strategy (5), although not a widely practiced technique (6). TH implies that increased $Paco_2$ might be a goal of therapy in critical illness, rather than its forceful disposition (1, 2) targeted by some other ventilatory techniques (6, 7).

*See also p. 2634.

Key Words: acid-base balance; hypercapnia; hypocapnia; lung injury; mechanical ventilation; permissive hypercapnia; therapeutic hypercapnia

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Dr. Laffey and colleagues (1–4) hypothesize that hypercapnic acidosis might have a direct protective effect in acute lung injury, independent of the ventilatory strategy employed. In contrast, hypocapnia may have a pathogenic role in the development of various central and peripheral disorders (3). Nonetheless, hypocapnia is purposely induced to treat intracranial hypertension in head trauma patients, during pulmonary hypertension in neonatal patients, and during induction of anesthesia. Hypocapnia also may occur accidentally due to excessive mechanical ventilation, extracorporeal membrane oxygenation, and high-frequency mode of ventilation (3). However, both hypocapnia and hypercapnia may have pathologic consequences (3, 8).

Dr. Laffey and colleagues (4) used an injurious ventilatory strategy (tidal volume of 12 mL/kg, positive end-expiratory pressure of 0 cm H_2O, frequency rate of 42/min) shown to produce significant lung stretch in rabbits. Experimental animals were treated with hypocapnic alkalosis, normocapnia, or TH ($Fico_2$ of 0, 0.05, and 0.12, respectively) over a 4-hr study period. This elegant study design showed that TH by itself can reduce lung injury despite maintaining the same injurious tidal volume in all groups. The authors noted that oxygenation was significantly improved when comparing hypocapnia with hypercapnia (an average reduction of 100 mm Hg in alveolar-arterial gradient). TH significantly increased plasma base excess and decreased dynamic lung compliance. In this study (4), Dr. Laffey and colleagues were able to reject their own hypothesis that the beneficial effect of TH may be related to alteration in surfactant biochemistry.

How does a waste product become a treasure? The possible protective mechanisms responsible for minimizing lung stretch by hypercapnia, in addition to the use of smaller tidal volumes and peak inspiratory pressure, have been elaborately discussed in a number of review articles by Dr. Laffey, Dr. Kavanagh (1–3, 9), and others (10–12). These include improved alveolar ventilation, a better V/Q matching, and consequent reduction in intrapulmonary shunt and increased systemic oxygenation. TH also can reduce deadspace ventilation and create the Bohr's effect (10, 13). In our laboratory, we have shown that TH can increase oxygen-carrying capacity of the blood in healthy ventilated dogs (11, 12). Other investigators have demonstrated that hypercapnia can be neuroprotective in immature rats subjected to hypoxic-ischemic brain damage, acting probably via some similar mechanisms, such as the Bohr's effect (14).

Does hypercapnia have a chance against established modes of ventilation? TH strategy, in the face of well-established traditional concepts, reminds me that it was only over a decade ago when we had a similar issue with two other endogenously produced and notoriously "toxic" gases, namely nitric oxide and CO. Since then, scientists have discovered the enormous biological properties of these two simple second messenger molecules in various biological systems. The question is, do we have a similar case with our universal metabolic waste product, CO_2? Currently, clinicians do not hesitate to say yes for NO (nitric oxide), and perhaps soon CO_2 will join the rest. Dr. Laffey and Dr. Kavanagh's research group have provided us with both experimental and theoretical evidence that hypercapnia is beneficial compared with hypocapnia (1–3, 9, 15). Other investigators have confirmed the efficacy of TH in animal models of acute lung injury (16, 17) or found deliberate hypercapnia to be deficient in terms of hemodynamic stability (18).

What else needs to be done? The limitations of this study have been fairly discussed by the authors (4). As they have noted, the critical issue of the study duration limits the applicability of their data for clinical purposes. Interventions may show different outcomes when applied at different stages of a disease. Therefore, a 4-hr experimental period is too short for a progressively developing ventilator-induced lung injury. Chronic exposures to hypercapnic environments are known to lead to adaptive changes in ventilation and acid-base balance, reflecting adjustments in control mechanisms of breathing and renal acidification mechanisms (8). Therefore, more animal studies are essential before any attempt to apply TH to critically ill patients. For example, dose-response curves for prolonged application of CO_2, as a drug, need to be established. Moreover, hemodynamic effects of TH are unknown, particularly for critically ill patients. It is also not clear if the benefits of TH are related to CO_2 or are pH mediated. Nonetheless, TH studies imply that permissive hypercapnia also could act not only indirectly via reduction in volume ventilation but perhaps directly through the effects of hypercapnia.

Dr. Laffey and colleagues (4) have raised concern regarding the safety of TH in the context of acute elevations in intracranial pressure or pulmonary vascular resistance. These are examples of cases that should be excluded for TH. At this stage, one can only speculate that some diseases involving lung injury and hypocapnia, such as sepsis, may specifically benefit from either TH or permissive hypercapnia.

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Vasopressin in septic shock: Clinical equipoise mandates a time for restraint*

Vasopressin use is rational in human septic shock. There is a vasopressin deficiency in septic shock, and vasopressin restores vascular tone in septic shock. Our group and others (1–12) showed that low-dose vasopressin (0.01–0.04 units/min) in vasodilatory shock decreases norepinephrine requirements, maintains blood pressure, and increases urine output. Thus, low-dose vasopressin could improve organ dysfunction and decrease mortality rate of septic shock.

In this issue, Dr. Klinzing and colleagues (13) evaluated vasopressin in septic shock by replacing norepinephrine with vasopressin to maintain blood pressure constant (mean vasopressin dose was 0.47 IU/min; range, 0.06–1.8 IU/min). Vasopressin decreased cardiac index, oxygen delivery, and oxygen uptake. Fractional splanchnic blood flow increased, yet the gastric P_{CO_2} gap increased. The authors conclude, and I agree, that "it would not appear beneficial to directly replace norepinephrine with vasopressin in septic shock." Dr. Klinzing and colleagues' study is important because it shows that simply replacing norepinephrine with vasopressin has deleterious consequences on global blood flow and complex effects on splanchnic perfusion. The dose of vasopressin was relatively high, making comparisons to low-dose vasopressin studies difficult. The unique strengths of Dr. Klinzing and colleagues' study include crossover from norepinephrine to vasopressin and measurement of splanchnic blood flow. Potential limitations are the small sample size (n = 12), lack of randomization, and controversy regarding the indocyanine green determination of splanchnic blood flow and the gastric P_{CO_2} gap.

Persistent vasodilation and failure to increase mean arterial pressure and cardiac output in response to resuscitation characterize nonsurvivors of septic shock. Oxygen delivery must be maintained above a critical threshold, and arterial pressure must be adequate. Catecholamines are most often used. Recent studies favor norepinephrine (14), but norepinephrine has important adverse effects. Norepinephrine's α-adrenergic effects decrease cardiac output, and norepinephrine at higher doses decreases renal blood flow and may decrease gut and myocardial perfusion. Norepinephrine increases pulmonary vascular resistance, and vascular responsiveness to norepinephrine diminishes.

Norepinephrine infusion results in nonphysiologic, high serum concentrations of norepinephrine. Yet mechanisms of cardiovascular dysfunction during sepsis are not directly related to catecholamines. For example, excessive activation of adenosine triphosphate-sensitive K^+ channels (15), which close voltage-dependent Ca^{2+} channels, decreases calcium entry and leads to widespread dilation of arterial smooth muscle independent of catecholamines.

Vasopressin has little effect on arterial pressure normally. Vasopressin acts primarily as an antidiuretic hormone. During hypotension, vasopressin levels increase and maintain arterial blood pressure by vasoconstriction (16). Vasopressin is secreted by the posterior pituitary. Activation of V_1 receptors on vascular smooth muscle causes vasoconstriction by blocking adenosine triphosphate-sensitive K^+ channels (17). Activation of V_2 receptors on renal tubules is responsible for water resorption, vasopressin's antidiuretic effect. Activation of V_3 pituitary receptors increases adrenocorticotropic hormone production (18). Vasopressin stimulates oxytocin receptors, which mediate vasodilation by stimulation of nitric oxide. Thus, there is organ-specific heterogeneity in the vascular responsiveness to vasopressin, and this vascular profile may be beneficial in septic shock. The study of Dr. Klinzing and colleagues (13) suggests potentially important differences between norepinephrine and vasopressin in gut blood flow distribution; however, the clinical impact is not clear in part because vasopressin increased gastric P_{CO_2} gap, which may indicate redistribution of blood flow away from the gut mucosa.

Patients with septic shock are sensitive to vasopressin (1, 4). Vasopressin stimulates V_1-mediated vasoconstriction and blocks adenosine triphosphate-sensitive K^+ channels (17). Vasopressin potentiates effects of catecholamines. Vasopressin-induced vasoconstriction spares cerebral, coronary, pulmonary, and afferent glomerular capillary circulations (19, 20).

Human studies of vasopressin in vasodilatory shock are summarized in Table 1. There are studies in patients who had septic shock (1–5, 13), in postbypass patients (6–10), and in organ donors with vasodilatory shock (11). We reported a case series of 50 patients who received vasopressin for >2 hrs for septic shock (2). Vasopressin (average dose 0.05 IU/min) increased blood pressure significantly. Cardiac index decreased slightly. Vasopressin increased urine output by nearly 80%. Total vasopressor dose decreased by 33% at 4 hrs and by about 50% thereafter. However, hospital mortality rate was 85%. There were six cardiac arrests in patients receiving vasopressin.

***See also p. 2646.**

Key Words: human septic shock; vasopressin; norepinephrine; spalchnic blood flow; cardiac output

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Table 1. Studies of low-dose vasopressin in human vasodilatory shock

Reference	Year	Study Type	No.	Patients	Endpoint Findings	Mortality Rate
Landry et al. (1)	1997	Case series	5	Septic shock	A, B, C	3/5
Landry et al. (4)	1997	Matched cohort	19	Septic shock	A, B, D in septic group	Not stated
			12	Cardiogenic shock		
Malay et al. (5)[a]	1999	RCT; placebo: N/S	10	Septic shock-trauma	A, B in treatment arm	0/5 in VP 2/5 in placebo
Argenziano et al. (7)	1998	Retrospective case series	40	Postbypass Vasodilatory shock	A, B, D	
Argenziano et al. (6)	1997	RCT; placebo: N/S	10	Vasodilatory shock Post-LVAD implantation	A, B in treatment arm D in all	Not stated
Argenziano et al. (8)	1999	Case series	20	Vasodilatory shock; postcardiac transplant	A, B	
Rosenzweig et al. (9)	1999	Case series	11	Pediatric-vasodilatory shock postbypass	A, B, D	2/11: low CO
Morales et al. (10)	2000	Retrospective case series	50	Vasodilatory shock post-LVAD implantation	A, B	Not stated
Chen et al. (11)	1999	Case series	10	Organ donors with vasodilatory shock	A, D	Not stated
Holmes et al. (2)	2001	Retrospective case series	50	Septic shock	A, B, C	84% (42/50)
Patel et al. (3)[a]	2002	RCT:VP vs. NE	24	Septic shock	A, B, C, D	Not stated
Klinzing et al. (13)	2003	Crossover: NE to VP	12	Septic shock	B	Not stated
Gold et al. (12)	2000	Case series	7	Milrinone-hypotension	A, B, C	Not stated

A, increase in blood pressure; B, decrease or discontinuance of catecholamines; C, increase in urine output; D, low plasma vasopressin levels in patients; RCT, randomized, controlled trial; VP, vasopressin; N/S, normal saline; LVAD, left ventricular assist device; CO, cardiac output; NE, norepinephrine.

[a]Randomized, controlled trials in septic shock.

These patients were all in severe refractory septic shock.

Only three studies of vasopressin were randomized, controlled trials of vasopressin: ten trauma patients in septic shock (5), ten patients who had vasodilatory shock after implantation of a left ventricular assist device (6), and 24 patients who had septic shock (3). Total number of subjects was only 44! Vasopressin increased blood pressure and decreased catecholamine infusion dose requirements in these studies.

Only two studies (3, 13) compared norepinephrine to vasopressin in septic shock. Dr. Klinzing and colleagues (13) did a single crossover study from norepinephrine to vasopressin; Patel et al. (3) reported a pilot double-blind randomized controlled trial of vasopressin vs. norepinephrine. In Patel et al.'s small trial, study drug (either vasopressin or norepinephrine) was titrated to maintain mean arterial pressure, and open label vasopressors (including open label norepinephrine) were titrated down. There were no changes in cardiac index, mean arterial pressure, or systemic vascular resistance index with either norepinephrine or vasopressin. In the norepinephrine group, norepinephrine infusion rate changed from 24 to 28 μg/min. In the vasopressin group (dose 0.06 units/min), the open norepinephrine infusion decreased from 30 to 8 μg/min in 1 hr. Vasopressin doubled the urine output and increased creatinine clearance. In contrast, norepinephrine did not change urine output or creatinine clearance. Vasopressin did not change gastric-arterial P_{CO_2} gradient.

The potentially beneficial effects of vasopressin in septic shock must be tempered with caution, because there are important examples of innovative treatments in critical care that had impressive results in early studies but in later studies were proved to increase mortality rate. Human growth hormone had strikingly positive effects on metabolic variables of critically ill adults. However, a randomized controlled trial showed that human growth hormone significantly increased mortality rate (21). Similarly, nitric oxide synthase inhibition by L-NG-methylarginine HCl increased mortality rate significantly in a multiple-center randomized controlled trial (22).

Because of these precedents, it is my impression that the vasopressin story is similar. There are beneficial short-term effects of vasopressin on hemodynamics and renal function in human septic shock; however, there are also potentially important adverse effects of vasopressin in human septic shock. Dr. Klinzing and colleagues' (13) study provides further insights into the limitations and adverse effects of vasopressin in septic shock. Thus, there is still true clinical equipoise regarding vasopressin in septic shock. I recommend restraint in clinical use of vasopressin until it (like human growth hormone and nitric oxide synthase inhibition) has been tested in a randomized controlled trial powered for mortality rate.

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Guidelines for critical care services and personnel—Innovations and improvements in patient care?*

Every system is perfectly designed to achieve the results it achieves.

Guidelines, recommendations, clinical pathways, or predefined standards of care may well be suitable to optimize the process of care (1), decrease resource utilization (2), limit practice variation (3), and promote the implementation of evidence-based medicine in critical care practice (4). However, serious concerns have been raised about their effect on patient outcomes (5), physician autonomy (6), and malpractice risks (7).

In medicine, practice guidelines should represent "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (8). There is support from both observational studies (9) and systematic reviews (10, 11) that, indeed, the process of guideline development will determine later acceptability by clinicians. In general, guidelines are more likely to be followed if they are evidence based (9) and were internally developed (10, 11). Controversial, vague, or nonspecific guidelines demanding extra resources, requiring new knowledge and skills, or provoking negative patient reactions are less likely to be adopted (9). Nevertheless, recommendations lacking formal evidence (i.e., solely based on expert opinion) may be of value as well (12) but need to be clearly specified and discussed as such.

The mindful reader of the "Guidelines on Critical Care Services and Personnel" (13) published in this issue of *Critical Care Medicine* has already noticed the considerable gap between the methodological requirements outlined previously and the recommendations presented by the Task Force of the American College of Critical Care Medicine of the Society of Critical Care Medicine.

However, in contrast to previous recommendations for the delivery of health care in the intensive care unit (14–16), the authors took the level of evidence (from randomized, prospective, controlled investigations to published opinion) of all citations into account. Although the task force compiled an impressive number of recommendations relevant to various areas of intensive care unit organization, the vast majority remain based on expert opinion only (13).

More important, the disclosure of uncertainty present in the wording of some recommendation may provoke criticism: Despite the fact that adherence to vague and nonspecific recommendations remains questionable, rigid guidelines with inflexible instructions (e.g., "The following physician subspecialties should be available and able to provide bedside care within 30 mins," or "The intensivist should be able to return more than 95%

***See also p. 2677.**

Key Words: guidelines; intensive care unit; process and organization; evidence-based medicine; methodology

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of pages within 5 mins") are only appropriate when there is good scientific evidence that the absence of these requirements will lead to harm for the patients (17). To prevent such misconceptions and false interpretations of individual recommendations, a specific labeling of the strength of evidence would have been desirable for all items.

In sharp contrast to scientifically sound clinical practice guidelines aimed toward therapeutic or diagnostic interventions (e.g., the regularly updated scientific statements of the American College of Cardiology and the American Heart Association) (18), the development of guidelines targeted toward organizational, personnel, and environmental requirements of intensive care units is hampered by the lack of strong scientific evidence. Despite the high level of activity and the rapidly evolving knowledge base in intensive care medicine, some of the most fundamental questions concerning the optimal organization of services to provide bedside critical care still remain vague. Only a few organizational aspects, including physician staffing (19), presence of an intensivist (20) and pharmacist rounds (21), have been demonstrated to be of benefit for patient care.

Does this mean the presented guidelines (13) are not worth considering? Unerringly not. Carefully interpreted, these guidelines may serve as an useful template that facilitates the analysis of the organizational *status quo* of intensive care units, thereby identifying strengths, weaknesses, and possible areas for process improvement (22). Guidelines themselves do not provide an approach for improvement. However, when used in conjunction with ambitious and explicitly defined aims, process-driven strategies may change systems, eventually leading to performance improvements (23).

Even when guidelines define optimal care and organizational standards, studies consistently demonstrate that guidelines alone are unlikely to be change physicians' behavior (6, 24). Most importantly, active involvement of all local care providers who will be responsible for implementing as well as executing the guidelines is required (25). Finally, evaluation studies and permanent follow-up are necessary to determine whether the guidelines are being used effectively and are improving processes and outcomes.

Guidelines will continue to have an increasing influence on the practice and evaluation of critical care medicine in the future. The uncontrolled enthusiasm for guidelines, and the sometimes unrealistic expectations about what they will accomplish, frequently betray inexperience and unfamiliarity with their limitations and potential hazards. When used appropriately, clinical practice guidelines can serve as an important adjunct to clinical research by facilitating the dissemination of new clinical findings and therefore can encourage innovations and improvements in patient care.

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Is adherence to clinical guidelines a good thing?*

Surveys of clinician adherence to clinical guidelines, like the one reported in this issue of *Critical Care Medicine* with nurses (1) and its preceding companion survey with physicians (2), assume it is desirable that clinicians comply with published guidelines, despite the fact that some clinical guidelines are weakly grounded and all are subject to being outdated when the newest, best evidence is reported. Respectively, the referenced surveys reviewed barriers to nurse and physician adherence to a review article on preventing ventilator-associated pneumonia (3).

In the nurse sample, the adherence rate was 78% to nonpharmacologic prevention strategies (1), equivalent to a 77% adherence rate among physicians (2). These high rates may be explained by sample selection bias. The response rate was 46% (n = 51) of 110 nurses attending critical care meetings who were given the survey (1). Comparisons of respondents with nonrespondents on demographics and other characteristics are not reported. No information is provided on how the survey was constructed, making it difficult to understand what was requested from the respondents and to evaluate the threat of socially desirable responses. The authors concluded that implementation of strategies to prevent ventilator-associated pneumonia is highly variable and suggested development of multinational guidelines to reduce variability. This recommendation is curious given the results of a consensus conference on ventilator-associated pneumonia led by a senior member of this investigative team (4). In that study, when 12 intensivist experts in ventilator-associated pneumonia were asked if they thought American Thoracic Society guidelines are acceptable for the treatment of ventilator-associated pneumonia, all 12 responded "no" and preferred instead the use of local guidelines. The methodological limitations of the present study, however, pale in comparison with assumptions underlying the study.

Despite the mantra that the randomized clinical trial provides a definitive test of efficacy, many clinical guidelines, including the narrative review on which the survey was based, do not describe adequately the methodological criteria used. The review article on prevention of ventilator-associated pneumonia (3) did not describe the search methods used to locate articles, explicit methods used to determine which articles to include in the review, and validity of the primary studies cited (5). Thus, publication bias, selection relevance, and reproducible decisions of the primary research cited—all criteria for a systematic review (6)—are potential problems and make it difficult for the reader to differentiate conclusions based on evidence from those based on the opinion of the author. Collectively, three articles (1–3) potentially have contributed to a weakly grounded evidence base for prevention of ventilator-associated pneumonia. Assessment of the strength of evidence for Kollef's conclusions (3) is beyond the scope of this editorial. Indeed, such an assessment may yield sound evidence. Moreover, there is little doubt that this investigative team has expertise in ventilator-associated pneumonia. Nevertheless, the team risks diluting the literature with expert opinion in contrast to rigorous evidence by failing to provide an audit trail of the evidence.

Ms. Ricart and colleagues (1) suggested that one value of clinical guidelines is reducing variability in practice. However, reference to nonadherence with guidelines frames bedside decision making in blind authority or expert opinion, two of the very traditions that evidence-based practice hopes to change. As advocated by Sackett et al. (7), evidence-based practice is patient-driven, not protocol-driven. Therefore, surveys might provide more meaningful information if they were constructed with patient scenarios that capture clinical variability within which guideline recommendations should be considered. Knowing the evidence and using it appropriately in a given patient context are not necessarily synonymous with guideline adherence.

For example, one strategy for preventing ventilator-associated pneumonia on the survey is semirecumbent positioning of the patient. Kollef (3) gave this strategy an evidence grade of B, defined as supported by at least one randomized, controlled investigation. Seventy-six percent of the nurses and 92% of the physicians reported adhering to this strategy (1). All of the 12% of nurses who reported nonadherence to semirecumbent positioning gave either adverse effects or patient comfort as reasons. We do not know the types of patients cared for by those who reported nonadherence with this strategy. Hemodynamic instability, for example, would require balancing an immediate threat to survival with the potential risk of aspiration. Positions other than semirecumbent, such as semiprone with the head down 15–20°, may provide alternatives to decrease the risk of aspiration. Theoretically, such a position promotes pulmonary drainage and reduces risk of aspiration because oropharyngeal and upper respiratory secretions are drained outward. Indeed, continuous subglottic suctioning, another strategy on the survey, may be unnecessary when the patient is in the semiprone head-down position. Although not all patients may tolerate alternative positions (8), the point here is that blind adherence to specific strategies is not desirable; constant risk-to-benefit assessment and variable strategies based on patient context are warranted to reduce morbidity rates and promote recovery (9).

If the survey captured the essence of evidence-based practice, the authors should be pleased with the adherence rate to nonpharmacologic strategies for preventing ventilator-associated pneumonia. If, however, the survey asked only if the nurse respondents adhered to the evidence, there is reason for concern. The findings then would suggest that the respondents practice in an undesirable way, steeped in blind authority and expert

*See also p. 2693.

Key Words: adherence; clinical guidelines; evidence-based practice; intensive care; position; ventilator-associated pneumonia

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opinion. This concern is supported by a qualitative study on use of the semirecumbent position for prevention of ventilator-associated pneumonia (10) conducted with intensive care unit clinicians in Canada. Nurse clinicians cited lack of physician order as the primary barrier to using the semirecumbent position. At least nurses in the survey by Ms. Ricart and colleagues (1) identified patient-driven reasons for nonadherence.

Attention to a rigorous audit trail of the evidence should be a primary concern in selecting clinical guidelines to promulgate, and clinicians should use guidelines as the term suggests—to *guide* bedside decision making. Blind adherence to clinical guidelines is undesirable because it removes patient context from decision making. Awareness of guidelines and the quality of foundational evidence are important. However, research on guideline adherence should capture the essence of evidence-based practice.

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