failure secondary to COPD exacerbation or congestive heart failure; in this setting, earlier extubation with the use of prophylactic NIV has yielded good results.

Prolonged MV and Tracheostomy From 5 to 13% of patients undergoing MV will go on to require prolonged MV (>21 days). In these instances, critical care personnel must decide whether and when to perform a tracheostomy. This decision is individualized and is based on the risk and benefits of tracheostomy and prolonged intubation as well as the patient's preferences and expected outcomes. A tracheostomy is thought to be more comfortable, to require less sedation, and to provide a more secure airway and may also reduce weaning time. However, tracheostomy carries the risk of complications, which occur in 5–40% of these procedures and include bleeding, cardiopulmonary arrest, hypoxia, structural damage, pneumothorax, pneumomediastinum, and wound infection. In patients with long-term tracheostomy, complex complications include tracheal stenosis, granulation, and erosion of the innominate artery. In general, if a patient needs MV for >10–14 days, a tracheostomy, planned under optimal conditions, is indicated. Whether it is completed at the bedside or as an operative procedure depends on local resources and experience. Some 5–10% of patients are deemed unable to wean in the ICU. These patients may benefit from transfer to special units where a multidisciplinary approach, including nutrition optimization, physical therapy with rehabilitation, and slower weaning methods (including SIMV with PSV), results in successful weaning rates of up to 30%. Unfortunately, close to 2% of ventilated patients may ultimately become dependent on ventilatory support to maintain life. Most of these patients remain in chronic care institutions, although some with strong social, economic, and family support may live a relatively fulfilling life with at-home ventilation.

FURTHER READING

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Section 2 Shock and Cardiac Arrest

296 Approach to the Patient with Shock

Anthony F. Massaro

Shock is the clinical condition of organ dysfunction resulting from an imbalance between cellular oxygen supply and demand. This life-threatening condition is common in the intensive care unit (ICU). There are a multitude of heterogeneous disease processes that can lead to shock. The organ dysfunction seen in early shock is reversible with restoration of adequate oxygen supply. Left untreated, shock transitions from this reversible phase to an irreversible phase and death from multisystem organ dysfunction (MSOF). The clinician is required to identify the patient with shock promptly, make a preliminary assessment of the type of shock present, and initiate therapy to prevent irreversible organ dysfunction and death. In this chapter, we review a commonly used classification system that organizes shock into four major types based on the underlying physiologic derangement. We discuss the initial assessment utilizing the history, physical examination, and initial diagnostic testing to confirm the presence of shock and determine the type of shock causing the organ dysfunction. Finally, we will discuss key principles of initial therapy with the aim of reducing the high morbidity and mortality associated with shock.

PATHOPHYSIOLOGY OF SHOCK

The cellular oxygen imbalance of shock is most commonly related to impaired oxygen delivery in the setting of circulatory failure. Shock can also develop during states of increased oxygen consumption or impaired oxygen utilization. An example of the impaired oxygen utilization is cyanide poisoning, which causes uncoupling of oxidative phosphorylation. This chapter will focus on the approach to the patient with shock related to inadequate oxygen delivery.

In the setting of insufficient oxygen supply, the cell is no longer able to support aerobic metabolism. With adequate oxygen, the cell metabolizes glucose to pyruvate, which then enters the mitochondria where ATP is generated via oxidative phosphorylation. Without sufficient oxygen supply, the cell is forced into anaerobic metabolism, in which pyruvate is metabolized to lactate with much less ATP generation (per mole of glucose). Maintenance of the homeostatic environment of the cell is dependent on an adequate supply of ATP. ATP-dependent ion pumping systems, such as the Na+/K+ ATPase, consume 20–80% of the cell's energy. Inadequate oxygen delivery and subsequent decreased ATP disrupt the cell's ability to maintain osmotic, ionic, and intracellular pH homeostasis. Influx of calcium can lead to activation of calcium-dependent phospholipases and proteases, causing cellular swelling and death. In addition to direct cell death, cellular hypoxia can cause damage at the organ system level via leakage of the intracellular contents into the extracellular space activating inflammatory cascades and altering the microvascular circulation.

DETERMINANTS OF OXYGEN DELIVERY

Since shock is the clinical manifestation of inadequate oxygen delivery compared to cellular needs, we will review determinants of oxygen delivery (DO_2). Disease processes affecting any of the components of oxygen delivery have the potential to lead to the development of shock. Disturbances to key determinants of oxygen delivery form the basis of the four major shock types described below.

The two major components of DO_2 are cardiac output (CO) and arterial oxygen content (CaO_2):

$$DO_2 = CO \times CaO_2$$

The two components of CO are heart rate (HR) and stroke volume (SV), which can be substituted in the above equation as

$$DO_2 = (HR \times SV) \times CaO_2$$

The major determinants of SV are preload, afterload (systemic vascular resistance, SVR), and cardiac contractility. The relationship can be represented as

$$SV \ \alpha \ (Preload \times contractility)/SVR$$

In this equation, preload refers to the myocardial fiber length before contraction (the ventricular end-diastolic volume). Contractility refers to the ability of the ventricle to contract independent of preload and afterload. The SVR represents the afterload, or the force against which the ventricle must contract.

The CaO_2 is composed of oxygen carried by convection with hemoglobin and oxygen dissolved in blood, given as

$$CaO_2 = (Hb \times 1.39 \times SaO_2) + (PaO_2 \times 0.03)$$

A disease process that affects these variables (HR, preload, contractility, SVR, SaO_2, or Hb) has the potential to reduce oxygen delivery and

cause cellular hypoxia. Each of the shock types described below has a distinctive physiologic hemodynamic profile corresponding with alterations in one of the variables affecting oxygen delivery described above.

CLASSIFICATION OF SHOCK

While there is a heterogeneous list of specific conditions that can cause shock, it is helpful to categorize these processes into four major shock types based on the primary physiologic derangement leading to reduced oxygen delivery and cellular hypoxia. The four major shock types are distributive, cardiogenic, hypovolemic, and obstructive. Table 296-1 outlines these major shock types as well as specific disease processes that can result in that physiologic derangement. Each shock type has a distinct hemodynamic profile (Table 296-2). Familiarity with the major shock types and their unique hemodynamic profile is essential so that when evaluating a patient presenting with shock, the clinician can use the history, physical examination, and laboratory testing to determine the type of shock present and promptly begin appropriate initial therapy to restore oxygen delivery.

Distributive Shock Distributive shock is the condition of reduced oxygen delivery where the primary physiologic disturbance is a reduction in SVR. It is unique among the types of shock in that there is a compensatory increase in CO (Table 296-2). The central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) are usually reduced. The most common cause of distributive shock is sepsis. Sepsis has recently been redefined as the dysregulated host response to infection resulting in life-threatening organ dysfunction. When this process is accompanied by persistent hypotension requiring vasopressor support, it is classified as septic shock. Other processes that are manifest as cellular hypoxia related to a primary reduction of SVR include pancreatitis, severe burns, and liver failure. Anaphylaxis is predominantly an IgE-mediated allergic reaction that can rapidly develop after exposure to an allergen (food, medication, or insect bite), in which there is a profound distributive type of shock possibly mediated through histamine release. In this setting, there is evidence of both venous and arterial vasodilation. Studies have demonstrated extravasation of up to 35% of the circulating blood volume within 10 min. Patients with severe brain or spinal cord injury may have a reduction of SVR related to disruption of the autonomic pathways that regulate vascular tone. In these patients, there is pooling of blood in the venous system with a resulting decreased venous return and decreased CO. A final category of patients who present with distributive shock are those with adrenal insufficiency. Adrenal insufficiency may be related to chronic steroid use, metastatic malignancy, adrenal hemorrhage, infection (tuberculosis, HIV), autoimmune adrenalitis, or amyloidosis. In conditions of stress (such as infection or surgery), the deficit may become apparent with an inability to increase cortisol leading to vasodilation as well as aldosterone deficiency-mediated hypovolemia.

TABLE 296-1 Pathophysiologic Classification of Shock

1. Distributive
   - a. Septic shock
   - b. Pancreatitis
   - c. Severe burns
   - d. Anaphylactic shock
   - e. Neurogenic shock
   - f. Endocrine shock
   - i. Adrenal crisis
2. Cardiogenic
   - a. Myocardial infarction
   - b. Myocarditis
   - c. Arrhythmia
   - d. Valvular
     - i. Severe aortic valve insufficiency
     - ii. Severe mitral valve insufficiency
3. Obstructive
   - a. Tension pneumothorax
   - b. Cardiac tamponade
   - c. Restrictive pericarditis
   - d. Pulmonary embolism
   - e. Aortic dissection
4. Hypovolemic
   - a. Hemorrhagic
   - b. GI losses
   - c. Burns
   - d. Polyuria
     - i. Diabetic ketoacidosis
     - ii. Diabetes insipidus

TABLE 296-2 Hemodynamic Characteristics of the Major Types of Shock

TYPE OF SHOCK	CVP	PCWP	CARDIAC OUTPUT	SYSTEMIC VASCULAR RESISTANCE
Distributive	↓	↓	↑	↓
Cardiogenic	↑	↑	↓	↑
Obstructive	↑	↓↑	↓	↑
Hypovolemic	↓	↓	↓	↑

Abbreviations: CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

Cardiogenic Shock Cardiogenic shock is characterized by reduced oxygen delivery related to a reduction in CO owing to a primary cardiac problem. There is usually a compensatory increase in SVR in cardiogenic shock. When the cardiac process (e.g., myocardial infarction) affects the left ventricle (LV), there will be elevation of the PCWP and when it affects the right ventricle (RV), the CVP will be elevated. As detailed above, the CO (and accordingly the DO_2) can be reduced by alterations in the SV or HR. In cardiogenic shock, the SV may be reduced by processes that affect myocardial contractility (myocardial infarction, ischemic cardiomyopathies, and primary myocarditis) or mechanical valvular disease (acute mitral insufficiency or aortic insufficiency). Both bradyarrhythmias and tachyarrhythmias (from either an atrial or ventricular source) may have associated hemodynamic consequence with a reduction in CO.

Hypovolemic Shock Hypovolemic shock encompasses disease processes that reduce CO (and oxygen delivery) via a reduction in preload. In addition to the reduced CO, this shock type is characterized by an elevated SVR and low CVP and PCWP related to decreased intravascular volume. Any process causing a reduction in intravascular volume can cause shock of this type. Hypovolemic shock most commonly is related to hemorrhage, that may be external (secondary to trauma) or internal (most commonly upper or lower gastrointestinal [GI]) bleeding. Hypovolemic shock can also be seen with nonhemorrhagic processes. Examples include GI illnesses causing profound emesis or diarrhea, renal losses (osmotic diuresis associated with diabetic ketoacidosis or diabetes insipidus), or skin loss (severe burns, inflammatory conditions such as Stevens-Johnson).

Obstructive Shock Obstructive shock is also characterized by a reduction in oxygen delivery related to reduced CO, but in this case the etiology of the reduced CO is an extracardiac processes impairing blood flow. Processes that can impede venous return to the heart and reduce CO include tension pneumothorax (PTX), cardiac tamponade, and restrictive pericarditis. Similarly processes that obstruct cardiac outflow, such as pulmonary embolism (right heart) or aortic dissection (left heart), are included in this shock type category.

Mixed Shock The types of shock outlined in this classification scheme are not mutually exclusive; not uncommonly, a patient will present with more than one type of shock. The initial physiologic disturbance leading to reduced perfusion and cellular hypoxia in sepsis is distributive shock. In this setting, a sepsis-induced cardiomyopathy

can develop, which reduces myocardial contractility, thus producing a cardiogenic component to what now would be described as a mixed type of shock.

Undifferentiated Shock Upon initial presentation, many patients have undifferentiated shock in which the shock type and specific disease process are not apparent. Using the history, physical examination, and initial diagnostic testing (including hemodynamic monitoring), the clinician attempts to classify a patient with one of the types of shock outlined above so that proper therapy can be initiated to restore tissue perfusion and oxygen delivery.

The type of shock seen most commonly is dependent upon the clinical area of practice. In the medical ICU, the largest number of patients have distributive shock related to sepsis. A cardiac ICU will have a population weighted toward cardiogenic or obstructive types of shock. The emergency department will see more of a mix of patients with trauma patients presenting with hypovolemic shock and septic patients having a distributive pathophysiology.

STAGES OF SHOCK

Regardless of type, shock progresses through a continuum of three stages. These stages are compensated shock (preshock), shock (decompensated shock), and irreversible shock. During compensated shock, the body utilizes a variety of physiologic responses to counteract the initial insult and attempts to reestablish the adequate perfusion and oxygen delivery. At this point, there are no overt signs of organ dysfunction. Laboratory evaluation may demonstrate mild organ dysfunction (i.e., elevated creatinine or troponin) or a mild elevation of lactate. The specific compensatory response is determined by the initial pathophysiologic defect. In early sepsis with reduction in SVR, there is a compensatory rise in HR (and CO). With early hemorrhagic volume loss, there will be a compensatory increase in SVR. As the host compensatory responses are overwhelmed, the patient transitions into true shock with evidence organ dysfunction. Appropriate interventions to restore perfusion and oxygen delivery during these initial two phases of shock can reverse the organ dysfunction. If untreated the patient will progress to the third phase of irreversible shock. At this point, the organ dysfunction is permanent and often the patient progresses to MSOF.

EVALUATION OF THE PATIENT WITH SHOCK

The evaluation of the patient with shock utilizes the history, physical examination, and diagnostic testing toward two specific aims. The first aim is confirmation of the presence of shock. Given the reversible nature of the organ dysfunction in early shock, it is important that the clinician has a high clinical suspicion for this condition. The possibility of shock should be considered all patients presenting with new organ dysfunction. This early recognition of the presence of shock is an essential tenet of shock care **(Table 296-3)**. A second aim of the initial assessment (history, physical examination, and diagnostic testing) is to identify either a specific shock etiology or to determine the type of shock present. We will discuss the role of the history, physical examination, and diagnostic testing toward these specific aims. While the assessment of shock etiology is ongoing, the initiation of therapy should not be delayed until the final diagnosis is determined. Evaluation of shock etiology and initiation of therapy should be simultaneous.

History Obtaining a concise, focused history is essential. If the patient is unable to provide a history, ancillary information from anyone accompanying the patient should be obtained, and a brief chart review should be performed. As the history is being obtained, the clinician must be attentive to any details indicating new organ dysfunction.

TABLE 296-3 Key Principles in the Treatment of Shock

1. Recognize shock early
2. Assess for type of shock present
3. Initiate therapy simultaneous with the evaluation into the etiology of shock
4. Restoration of oxygen delivery is the aim of therapy
5. Identify etiologies of shock which require additional lifesaving interventions

The most easily identified new organ dysfunction from the history is the presence of a newly altered mental status or decrease in renal function (oliguria). In some cases, the type of shock (and the specific disease process) is apparent from the history. Patients with distributive shock from sepsis may present with fever and a history revealing of a focal site of infection. Anaphylactic distributive shock may be suggested by the onset of hives, dyspnea, and new facial edema after exposure to common allergens. Cardiogenic shock may be identified by the onset of exertional chest discomfort. The patient with significant arrhythmia may have an initial complaint of palpitations with syncope or presyncope. Hypovolemic shock may be identified in patients who present with a history of trauma (blunt or penetrating) or GI bleed (hematemesis, melena, or bright red blood per rectum). A patient with hypertension and tearing chest or back pain may be presenting with acute aortic dissection and obstructive type shock. Acute onset chest pain with dyspnea in the setting of immobility and or underlying malignancy raises concern for obstructive shock due to pulmonary embolism.

For most patients, the specific etiology will be less clear but the history can be helpful in raising the likelihood of a particular type of shock. As an example, a patient with a preexisting immune dysfunction or medication-induced neutropenia may present with hypoperfusion and new organ dysfunction, in which the clinician must have a high suspicion for septic shock. Similarly, a patient with extensive cardiac disease requires a higher suspicion for cardiogenic shock.

Physical Examination The physical examination should be conducted with the aim of answering two questions. Is shock present (either in compensated stage prior to overt evidence of organ dysfunction or decompensated indicated by the presence of new organ dysfunction)? Secondly, what type of shock is present (distributive, cardiogenic, hypovolemic, or obstructive)?

The physical examination findings present during the compensated phase of shock tend to be nonspecific. These include an elevation of the HR (with the body's attempt to increase CO) or tachypnea (to compensate for the developing metabolic acidosis). While nonspecific, the clinician should recognize these findings early as they may herald the development of end-organ dysfunction if perfusion and oxygen delivery are not restored. Shock is most commonly seen in the setting of circulatory failure. In most cases, this is manifest as hypotension (a mean arterial pressure [MAP] of <60 mmHg), but this finding is not always present. Many patients may have underlying conditions that cause longstanding low blood pressure without any evidence of organ dysfunction. Alternatively, patients with underlying hypertension may develop organ dysfunction at higher blood pressures.

The physical examination can confirm the presence of shock prior to the return of laboratory testing. The central nervous system (CNS), kidney, and skin are the organ systems most easily assessed for evidence of organ dysfunction. These organ systems are considered the "windows" through which we can identify organ dysfunction. Decreased oxygen delivery to the brain is manifest as confusion and encephalopathy. In the early stage of shock, the body will redirect blood flow to the CNS to maintain adequate perfusion. In the patient with shock and altered mental status, all the usual compensatory mechanisms have been outstripped by the magnitude of shock pathophysiology. New encephalopathy represents decompensated shock. To assess renal function during the physical examination, one should evaluate the patient's urine output since the time of presentation. If not already present, a urinary catheter should be placed for accurate hourly assessment of urine output. In patients with normal baseline renal function, oliguria (<0.5 mL/kg per h) may indicate shock. Finally, decreased capillary refill and cold and clammy skin are signs of hypoperfusion and shock.

Many components of the examination provide insight into hemodynamics and assist in elucidating the type of shock present. Evaluation of jugular venous pressure (JVP) and peripheral edema can provide insight into right-sided cardiac pressures. Pulmonary auscultation can identify signs of left-sided cardiac dysfunction. The physical examination may be used to differentiate shock with high CO (distributive) from that with low CO (cardiogenic shock, hypovolemic shock, and obstructive shock). Examination findings suggestive of high output

shock (distributive) include warm peripheral extremities, brisk capillary refill (<2 s), and bounding pulses. Alternatively, cool extremities, delayed poor capillary refill, or weak pulses would indicate low CO forms of shock. Among those with evidence of low CO, the examination can be used to distinguish between conditions with increased intravascular filling pressure (cardiogenic shock) and intravascular volume depletion (hypovolemic shock). The JVP may be elevated cardiogenic shock (with right-sided failure) and reduced (JVP <8 cm) in hypovolemic shock. The presence of cardiogenic shock would be further supported by an S3 gallop. One must remember, however, that it is well established that patients with chronic heart failure do not present with the classical findings of acute heart failure.

At times, the physical examination may identify the specific etiology of shock. This is particularly helpful in the patient who cannot provide a detailed history. The examination may demonstrate the site of an untreated infection (cellulitis, abscess, infected pressure injury, or focal). The examination may reveal a brady- or tachyarrhythmia leading to development of shock. Similarly, large ecchymosis may indicate a significant bleed related to trauma or spontaneous retroperitoneal bleeding. The rectal examination may reveal GI hemorrhage. Pulsus paradox and elevated JVP may suggest the presence of cardiac tamponade. Patients with a tension PTX may have a paucity of breath sounds over the affected side, deviation of the trachea away from the affected side, or subcutaneous emphysema.

Combinations of easily assessed examination components have been combined to create a scoring system to identify high risk patient populations. The shock index (SI) is defined as the HR/systolic blood pressure (SBP) with a normal SI being 0.5–0.7. An elevated SI (>0.9) has been proposed to be a more sensitive indicator of transfusion requirement and of patients with critical bleeding among those with hypovolemic (hemorrhagic) shock than either HR or BP alone. The SI may also identify patients at risk for postintubation hypotension. This concept of use of a clinical score to identify at-risk patients has been extended to patients with distributive shock from sepsis. The quick Sequential Organ Failure Assessment (qSOFA) score is a rapid assessment scale that assigns a point for SBP <100, respiratory rate >22, or altered mental status (Glasgow Coma Scale <15). A qSOFA ≥2 (with a concern for infection) is associated with a significantly greater risk of death or prolonged ICU stay. The Third International Consensus Definition of Sepsis has recommended the use of the qSOFA to identify the most acutely ill subset of patients with sepsis (longer length of stay, increased need for ICU admission, and higher in-hospital mortality).

Diagnostic Testing Laboratory evaluation should be initiated promptly in all patients with suspected shock. The laboratory evaluation is directed toward the dual aim of assessing the extent of end-organ dysfunction and of gaining insight into the possible etiology of shock. Table 296-4 outlines the recommended initial laboratory evaluation of the patient with undifferentiated shock.

BLOOD TESTS Evaluation of blood urea nitrogen (BUN), creatinine, and transaminases provide an assessment of the extent of end-organ dysfunction related to shock. Urine electrolytes with subsequent calculation of the fractional excretion of sodium (FENa) or fractional excretion of urea (FEUrea) may indicate states of hypovolemia or decreased effective circulating volume. Elevation of alkaline phosphatase may suggest biliary obstruction and may thereby identify a source of infection in patients with distributive shock. Elevation of cardiac enzymes can indicate a primary cardiac problem with myocyte damage related to ischemia, myocarditis, or a pulmonary embolism. An elevation of the white blood cell count may raise suspicion for an infective process, but this is certainly not diagnostic; an accompanying left shift may improve the sensitivity of this measure. While the extent of acidosis may be determined with a venous blood gas (VBG), if there is accompanying hypoxemia an arterial blood gas should be obtained. For patients with undifferentiated shock, there should always be a high index of suspicion for possible infection. Urinalysis and urine sediment should be sent to evaluate for pyuria. Blood cultures, urine cultures, and sputum cultures should be obtained. Radiographic evaluation should be directed to seek sources of infection suggested by the history and physical examination.

TABLE 296-4 Initial Laboratory Evaluation of Undifferentiated Shock

1. Lactate
2. Renal function tests
3. Liver function tests
4. Cardiac enzymes
5. Complete blood count (with differential)
6. PT, PTT, and INR
7. Urinalysis and urine sediment
8. Arterial blood gas
9. ECG

Abbreviations: INR, International normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

Lactate measurement has a role in the diagnosis, risk stratification, and, potentially, the treatment of shock. Increased lactate (hyperlactemia) and lactic acidosis (hyperlactemia and pH <7.35) are common in shock. Lactate is a product of anaerobic glucose metabolism. In glycolysis, the enzyme phosphofuctokinase metabolizes glucose to pyruvate. Under aerobic conditions, the pyruvate is then converted (in the mitochondria) to acetyl CoA and enters the Krebs cycle with resulting ATP generation through oxidative phosphorylation. In the setting of cellular hypoxia, the Krebs (tricarboxylic acid) cycle cannot oxidize the pyruvate, and thus, the pyruvate is converted to lactate by the enzyme lactate dehydrogenase. Under normal conditions, lactate is produced from skeletal muscle, brain, skin, and intestine. In the setting of reduced oxygen delivery and cellular hypoxia, the amount of lactate produced from these tissues increases (and other tissue can begin to produce lactate). While most of the studies have been performed in patients with septic shock, there is evidence that elevated lactate correlates with a worse outcome. A recent systematic literature review evaluating the role of lactate measurement in a variety of critically ill populations supported the value of serial lactate measurements in the evaluation of critically ill patients and their response to therapy.

ECG The electrocardiogram (ECG) is an essential part of the evaluation of the patient with shock. There may be a bradycardia or tachycardic arrhythmia causing a reduction in CO. ST segment elevation myocardial infarction may be identified. The presence of the S1 Q3 T3 pattern would raise concerns for pulmonary embolism. Reduced voltage in the presence of electrical alternans raises the possibility of pericardial tamponade.

Echocardiography Echocardiography is increasingly used as an essential tool to help categorize shock, and it provides an assessment that is both rapid and noninvasive. Familiarity with basic echocardiographic techniques and interpretation is now expected in the critical care setting. Accordingly, competency standards have been proposed for critical care providers in both basic and advanced echocardiographic techniques. The bedside echocardiogam performed by the ICU team does not replace a formal examination performed by the echocardiography service.

The basic echocardiographic assessment for the shock patient is transthoracic echocardiography (TTE) utilizing both the two-dimensional (2D) and M mode. Standardized, focused echocardiography protocols such as the RACE protocol (rapid assessment for cardiac echocardiography) have been introduced to facilitate the assessment of cardiac function. It focuses the examination on LV function, RV function, and pericardium. It also can assess volume, but the use of echocardiography for volume assessment will be discussed in the section below.

The 2D mode can evaluate LV size, wall thickness, and ventricular function. Ventricular size and thickness can suggest longer standing cardiac processes. Evaluation of LV function through estimation of left ventricular ejection fraction (LVEF), and can identify shock with globally reduced LV function or regional wall motion abnormalities. Similarly, the assessment of RV function also examines RV size and wall thickness (to identify conditions such as elevated pulmonary pressures or suggest pulmonary embolism), and also evaluate the patient for pericardial tamponade. Two-dimensional echocardiography can

also be used to assess valve function, including acute processes, such as mitral valve rupture. Assessment of valvular function is often a process that requires a higher skilled practitioner. The performance of the bedside echocardiogram by the critical care practitioner does not replace formal assessment by a cardiologist.

INITIAL TREATMENT OF SHOCK

Since shock can progress rapidly to an irreversible stage, a key principle in shock management is to initiate treatment for circulatory shock simultaneous with efforts to elucidate shock etiology (Table 296-3). If the initial history, physical examination, and laboratory evaluation have identified the shock type or the specific etiology, then therapy is directed to reverse the underlying physiologic abnormality causing the hypoperfusion and reduced oxygen delivery. Details of the optimal care for the specific disease processes leading to shock may be found in other chapters of this text. As many patients will present with undifferentiated shock, in this section we will discuss treatment directed at the patient with undifferentiated shock. At the conclusion of this section, we will highlight etiologies of shock that require initiation of lifesaving specific therapy.

The development of shock is a medical emergency, and optimal therapy involves the involvement of a multidisciplinary team to allow the evaluation and initiation of therapy to begin simultaneously. Patients must be treated in a setting where adequate resources are available to support frequent reassessments and invasive monitoring. Most patients with shock should be cared for in an ICU setting.

A key early consideration is to ensure adequate intravenous access. Placement of a peripheral venous catheter (16G or 18G) will provide initial access for the aggressive volume resuscitation that is required for patients with distributive or hypovolemic shock. If there is concern for distributive shock with sepsis, this IV access will also permit prompt antibiotic administration. For patients with ongoing hypotension despite adequate volume resuscitation, placement of a central venous catheter (CVC) is indicated to provide therapy with vasopressors and inotropes. The CVC will provide a mechanism for hemodynamic monitoring (CVP) as well as a means to obtain central venous oxygen saturations ($ScvO_2$). The $ScvO_2$ is a surrogate of mixed venous oxygen saturation, and, thus, can provide insight into the adequacy of oxygen delivery. Central venous access using a sheath will provide an access point for placement of a Swan Ganz catheter if more detailed assessment of hemodynamic measurements are required (PCWP, CO, and SVR). If the patient presents critically ill or in the midst of cardiopulmonary arrest, the quickest method of obtaining central access will be through the use of an intraosseous device. Placement of an arterial line allows for intravascular measurement of blood pressure and continuous determination of MAP. In addition, it can provide insight into the adequacy of volume resuscitation through the measurement of systolic or pulse pressure variation. The arterial line will provide access for determination of arterial oxygen tension, which is helpful since peripheral oximetry measurements (SpO_2) can be unreliable in states of tissue hypoperfusion. The arterial line facilitates repeated measures of acid base status or lactate to assess the impact of treatment. All patients with shock should have a urinary catheter placed to permit hourly assessment of renal function as another potential indication of the adequacy of resuscitation

Volume Resuscitation Initial volume resuscitation has the aim of restoring tissue perfusion and is crucial to optimal shock therapy. Assessment of current intravascular volume status and determination of the optimal amount of volume resuscitation are challenging. The physiologic goal of volume resuscitation is to move the patient to the nonpreload-dependent portion of the Starling curve. Most patients with any of the four shock types will benefit from an increase in intravascular volume. For patients with distributive shock, the need for early aggressive volume replacement is well established. In the past, the use of early goal-directed therapy (EGDT) in septic shock targeted specific measures of CVP, MAP, and SvO_2 to guide volume resuscitation (and initiation of vasopressors and inotropes). More recent studies have demonstrated that targeted resuscitation using invasive monitoring is not required, but in all of these studies patients in the "usual care" arms of the study received early initial volume resuscitation. For patients with suspected septic shock, a minimum of 30 mL/kg is recommended by the Surviving Sepsis Campaign. While the need for volume resuscitation is most apparent for patients with distributive or hypovolemic shock, even patients with cardiogenic shock may benefit by cautious volume replacement. In these patients, there should be a careful assessment of volume status prior to volume administration.

In general, volume replacement therapy should be given as a bolus with a predefined endpoint to assess the effect of the volume resuscitation. Most commonly, the volume resuscitation will begin with crystalloid. In patients with hypovolemic shock due to ongoing hemorrhage, volume replacement with packed red blood cells is warranted. In cases of massive transfusion, platelets and fresh frozen plasma should be provided to offset the dilution of these components during volume replacement. Since hemoglobin is a key determinant of $CaCO_2$ red cell administration may be a part of volume replacement even without hemorrhage if hemoglobin content is <7 g/dL in order to optimize oxygen delivery.

Assessment of intravascular volume status (and the adequacy of volume resuscitation) begins with the physical examination (described above). The passive leg raise (PLR) test can predict responsiveness to additional intravenous fluid (IVF) by providing the patient with an endogenous volume bolus. While the patient is resting in a semirecumbent position at a 45-degree angle, the bed is placed in trendelenburg such that the patient's head becomes horizontal and the legs are extended at a 45-degree angle. There is then an immediate (within 1 min) assessment of changes in CO (or pulse pressure variation as a surrogate). It is important to emphasize that one does not merely look for changes in blood pressure; if the shock patient is mechanically ventilated there is the option of looking at changes in SV variation (or pulse pressure variation) during the respiratory cycle to assess volume responsiveness. A >12% SV variation suggests a volume-responsive state. This measurement requires that the patient be in a volume cycle mode of ventilation, without breath-to-breath variations in intrathoracic pressure and without arrhythmias. A final caveat to the use of these parameters to assess volume status is that these studies are performed on patients being ventilated with tidal volumes larger than currently used to minimize ventilator-induced lung injury.

There is also increased use of echocardiography to assist in determination of intravascular fluid status, with a variety of static and dynamic variables that the trained operator can assess. The most commonly used parameters to assess adequacy of volume resuscitation are inferior vena cava (IVC) diameter and IVC collapse. Alternatively, serial assessments of LV function can be performed while volume is being administered. Placement of a pulmonary artery catheter (PAC) is another tool for assessment of volume status. This more invasive measure involves placement of the PAC into the central venous circulation and through the right heart. Ports in the PAC (Swan Ganz catheter) allow for direct measurement of CVP, pulmonary artery (PA), and PCWPs. The PCWP is used as a surrogate for LA pressure. While studies have not identified a mortality or length-of-stay benefit with routine use of PA catheterization, there are cases where it may be beneficial. Patients with mixed shock (distributive and cardiogenic) or those with ongoing shock of unclear etiology are examples of situations in which it should be considered.

The need for continued volume replacement must be frequently reassessed. As the patient continues to receive treatment for shock, the initial proper strategy regarding volume management may change in light of development of processes that independently require a different volume management strategy. For patients who initially present with shock but then develop failure related to acute respiratory distress syndrome (ARDS) or renal failure, it may be reasonable to begin volume removal.

Vasopressor and Inotropic Support If intravascular volume status has been optimized with volume resuscitation but hypotension and inadequate tissue perfusion persist, then vasopressor and inotropic support should be initiated. The use of vasopressors and inotropes must be tailored to the primary physiologic disturbance. The clinician

must understand the receptor selectivity of various agents and that for some agents the selectivity may be dose-dependent. In patients with distributive shock, the aim is to increase the SVR. Norepinephrine is the first choice vasopressor: with potent α_1 and β_1 adrenergic effects. The α_1 causes vasoconstriction while β_1 has positive inotropic and chronotropic effects. At high doses, epinephrine has a similar profile (at lower doses the β effects predominate), but is associated with tachyarrhythmia, myocardial ischemia, decreased splanchnic blood flow, pulmonary hypertension, and acidosis. In distributive shock, vasopressin deficiency may be present. Vasopressin acts on the vasopressin receptor to reverse vasodilation and redistribute flow to the splanchnic circulation. In a randomized trial in patients with septic shock, the addition of low-dose vasopressin did not reduce all-cause 28-day mortality compared to norepinephrine. Vasopressin is safe and has a role as a second agent for hypotension in septic shock. Dopamine does not have a role as a first line agent in distributive shock. A randomized control study in patients with all cause circulatory shock did not show a survival benefit, but did reveal an increase in adverse events (arrhythmia). In this study, the subgroup of patients with cardiogenic shock had increased mortality. For patients with cardiogenic shock, dobutamine is the first line agent; it is a synthetic catecholamine with primarily β-mediated effects and minimal α adrenergic effects. The β_1 effect is manifest in increased inotropy and the β_2 effect leads to vasodilation with decreased afterload; it can be used with norepinephrine in patients with mixed distributive and cardiogenic shock.

OXYGENATION AND VENTILATION SUPPORT

In addition to the cellular hypoxia caused by the circulatory failure, patients with shock may present with hypoxemia. For patients with distributive shock, this may be related to a primary pulmonary process (pneumonia in a patient with septic shock). For patients with cardiogenic or obstructive shock, the hypoxemia may be related to LV dysfunction and elevations of PCWP. For patients with all types of shock, there can be development of ARDS and subsequent $\dot{V}/\dot{Q}$ mismatch and shunt. Supplemental oxygen should be initiated and titrated to maintain SpO_2 of 92–95%. This may require intubation and initiation of mechanical ventilation. If the patient requires intubation and initiation of mechanical ventilation, this should be provided promptly so as to minimize the duration of tissue hypoxia. Patients with shock may have high minute ventilatory needs to compensate for metabolic acidosis. As shock progresses, they may not be able to maintain adequate respiratory compensation, which may be a second indication to initiate mechanical ventilator support. If mechanical support is initiated, it is important to provide ventilation with lung-protective strategies focused on low tidal volume ventilation and optimization of positive end-expiratory pressure to minimize ventilator-induced lung injury. In addition, there should be daily sedation cessation to assess underlying neurologic function and minimize time on mechanical ventilation. There are currently little data to support the use of noninvasive ventilation in the setting of shock.

Antibiotic Administration Sepsis and septic shock are the most common cause of shock. For patients presenting with undifferentiated shock, if the diagnosis of septic shock is being entertained then broad spectrum antibiotics should be administered after obtaining appropriate cultures. For patients with sepsis, every hour delay in antibiotic administration is associated with an increase in mortality. While it is ideal to initiate antibiotics after appropriate cultures, the inability to obtain cultures should not delay the start of treatment. When sepsis is excluded as a cause of shock, an important aspect of antibiotic stewardship is to stop all antibiotics.

Specific Causes of Shock Requiring Tailored Intervention The initial evaluation (history, physical examination, and diagnostic testing) may have identified an etiology of shock that requires urgent lifesaving intervention in addition to the initial treatment steps outlined above. Patients with distributive shock secondary to anaphylaxis require removal of the inciting allergen, administration of epinephrine, and vascular support with intravenous fluid resuscitation and vasopressors. Adrenal insufficiency requires replacement with intravenous stress dose steroids. Cardiogenic shock patients with arrhythmia may require treatment as outlined in advanced cardiac life support algorithms or placement of an artificial pacemaker. In cases of acute ischemic events, consideration must be given to revascularization and temporary mechanical supportive measures. In the case of valve dysfunction, emergency surgery may be considered. Patients with hypovolemic shock due to hemorrhage may require surgical intervention in the case of trauma or endoscopic or interventional radiology procedures in the case of a GI source of blood loss. Among patients with obstructive shock, a tension PTX would necessitate immediate decompression. Proximal pulmonary embolism requires evaluation for thrombolytic therapy or surgical removal of the clot. Dissection of the ascending aorta may require surgical intervention.

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297 Sepsis and Septic Shock

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INTRODUCTION AND DEFINITIONS

Sepsis is a common and deadly disease. More than two millennia ago, Hippocrates wrote that sepsis was characterized by rotting flesh and festering wounds. Several centuries later, Galen described sepsis as a laudable event required for wound healing. Once the germ theory was proposed by Semmelweis, Pasteur, and others in the nineteenth century, sepsis was recast as a systemic infection referred to as "blood poisoning" and was thought to be due to pathogen invasion and spread in the bloodstream of the host. However, germ theory did not fully explain sepsis: many septic patients died despite successful removal of the inciting pathogen. In 1992, Bone and colleagues proposed that the host, not the germ, was responsible for the pathogenesis of sepsis. Specifically, they defined sepsis as a systemic inflammatory response to infection. Yet sepsis arose in response to many different pathogens, and septicemia was neither a necessary condition nor a helpful term. Thus, these investigators instead proposed the term *severe sepsis* to describe cases where sepsis was complicated by acute organ dysfunction and the term *septic shock* for a subset of sepsis cases that were complicated by hypotension despite adequate fluid resuscitation along with perfusion abnormalities.

In the past 20 years, research has revealed that many patients develop acute organ dysfunction in response to infection but without a measurable inflammatory excess (i.e., without the systemic inflammatory response syndrome [SIRS]). In fact, both pro- and anti-inflammatory responses are present along with significant changes in other pathways. To clarify terminology and reflect the current understanding of the pathobiology of sepsis, the Sepsis Definitions Task Force in 2016 proposed the Third International Consensus Definitions specifying that *sepsis* is a dysregulated host response to infection that leads to acute organ dysfunction. This definition distinguishes sepsis from uncomplicated infection that does not lead to organ dysfunction, a poor course,

TABLE 297-1 Definitions and Criteria for Sepsis and Septic Shock

CONDITION	DEFINITION	COMMON CLINICAL FEATURES	CRITERIA IN 1991/2003 ("SEPSIS-1"/"SEPSIS-2")	CRITERIA IN 2016 ("SEPSIS-3")
Sepsis	A life-threatening organ dysfunction caused by a dysregulated host response to infection	Include signs of infection, with organ dysfunction, plus altered mentation; tachypnea; hypotension; hepatic, renal, or hematologic dysfunction	Suspected (or documented) infection plus ≥2 systemic inflammatory response syndrome (SIRS) criteria[a]	Suspected (or documented) infection and an acute increase in ≥2 sepsis-related organ failure assessment (SOFA) points[b]
Septic shock	A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities lead to substantially increased mortality risk	Signs of infection, plus altered mentation, oliguria, cool peripheries, hyperlactemia	Suspected (or documented) infection plus persistent arterial hypotension (systolic arterial pressure, <90 mmHg; mean arterial pressure, <60 mmHg; or change in systolic by >40 mmHg from baseline	Suspected (or documented) infection plus vasopressor therapy needed to maintain mean arterial pressure at ≥65 mmHg and serum lactate >2.0 mmol/L despite adequate fluid resuscitation

[a]SIRS criteria include 1 point for each of the following (score range, 0–4): fever >38°C (>100.4°F) or <36°C (<96.8°F); tachypnea with >20 breaths per min; tachycardia with heart rate >90 beats per min; leukocytosis with white blood cell count >12,000/μL; leukopenia (<4000/μL) or >10% bands. [b]SOFA score is a 24-point measure of organ dysfunction that uses six organ systems (renal, cardiovascular, pulmonary, hepatic, neurologic, hematologic), where 0–4 points are assigned per organ system.

or death. In light of the wide variation in the ways that septic shock is identified in research, clinical, or surveillance settings, the Third International Consensus Definitions further specified that *septic shock* be defined as a subset of sepsis cases in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality risk.

To aid clinicians in identifying sepsis and septic shock at the bedside, new "Sepsis-3" clinical criteria for sepsis include (1) a suspected infection and (2) acute organ dysfunction, defined as an increase by two or more points from baseline (if known) on the sequential (or sepsis-related) organ failure assessment (SOFA) score **(Table 297-1)**. Criteria for septic shock include sepsis plus the need for vasopressor therapy to elevate mean arterial pressure to ≥65 mmHg with a serum lactate concentration >2.0 mmol/L despite adequate fluid resuscitation.

ETIOLOGY

Sepsis can arise from both community-acquired and hospital-acquired infections. Of these infections, pneumonia is the most common source, accounting for about half of cases; next most common are intraabdominal and genitourinary infections. Blood cultures are typically positive in only one-third of cases, while many cases are culture negative at all sites. *Staphylococcus aureus* and *Streptococcus pneumoniae* are the most common gram-positive isolates, while *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa* are the most common gram-negative isolates. In recent years, gram-positive infections have been reported more often than gram-negative infections, yet a 75-country point-prevalence study of 14,000 patients on intensive care units (ICUs) found that 62% of positive isolates were gram-negative bacteria, 47% were gram-positive bacteria, and 19% were fungi.

The many risk factors for sepsis are related to both the predisposition to develop an infection and, once infection develops, the likelihood of developing acute organ dysfunction. Common risk factors for increased risk of infection include chronic diseases (e.g., HIV infection, chronic obstructive pulmonary disease, cancers) and immunosuppression. Risk factors for progression from infection to organ dysfunction are less well understood but may include underlying health status, preexisting organ function, and timeliness of treatment. Age, sex, and race/ethnicity all influence the incidence of sepsis, which is highest at the extremes of age, higher in males than in females, and higher in blacks than in whites. The differences in risk of sepsis by race are not fully explained by socioeconomic factors or access to care, raising the possibility that other factors, such as genetic differences in susceptibility to infection or in the expression of proteins critical to the host response, may play a role.

EPIDEMIOLOGY

The incidences of sepsis and septic shock depend on how acute organ dysfunction and infection are defined as well as on which data sources are studied. Disparate estimates come from administrative data, prospective cohorts with manual case identification, and large electronic health-record databases. Organ dysfunction is often defined by the provision of supportive therapy, in which case epidemiologic studies count the "treated," rather than the actual, incidence. In the United States, recent cohort studies using administrative data suggest that upwards of 2 million cases of sepsis occur annually. Shock is present in ~30% of cases, resulting in an estimated 230,000 cases in a recent systematic review. An analysis of data (both clinical and administrative) from 300 hospitals in the United Healthcare Consortium estimated that septic shock occurred in 19 per 1000 hospitalized encounters. The incidences of sepsis and septic shock are also reported to be increasing (according to ICD9-CM diagnosis and procedure codes), with a rise of almost 50% in the past decade. However, the stability of objective clinical markers (e.g., provision of organ support, detection of bacteremia) over this period in a two-center validation study suggests that new ICD-9 coding rules, confusion over semantics (e.g., *septicemia* versus *severe sepsis*), rising capacity to provide intensive care, and increased case-finding confound the interpretation of serial trends. Studies from other high-income countries report rates of sepsis in the ICU similar to those in the United States.

While the data demonstrate that sepsis is a significant public-health burden in high-income countries, its impact on the populations of low- and middle-income countries is probably even more substantial because of the increased incidence of infectious diseases and the high prevalence of HIV in some parts of the developing world. Although there are fewer high-quality studies on sepsis in these countries, the available data support sepsis as a major public-health problem. For example, a study of one cohort in rural Uganda found an incidence of laboratory-confirmed sepsis tenfold that of current global sepsis estimates; as only a minority of patients with sepsis develop bacteremia, the incidence of sepsis in the cohort was probably even higher. Case–fatality rates in low- and middle-income countries are also higher than those in high-income countries, as exemplified by two observational cohorts in Brazil with mortality rates >40%.

PATHOGENESIS

For many years, the clinical features of sepsis were considered the result of an excessive inflammatory host response (SIRS). More recently, it has become apparent that infection triggers a much more complex, variable, and prolonged host response than was previously thought. The specific response of each patient depends on the pathogen (load and virulence) and the host (genetic composition and comorbidity), with different responses at local and systemic levels. The host response evolves over time with the patient's clinical course. Generally, proinflammatory reactions (directed at eliminating pathogens) are responsible for "collateral" tissue damage in sepsis, whereas anti-inflammatory responses are implicated in the enhanced susceptibility to secondary infections that occurs later in the course. These mechanisms can be characterized as an interplay between two "fitness costs": direct damage to organs by the pathogen and damage to organs stemming from the host's immune response. The host's ability to resist as well as tolerate both direct and immunopathologic damage will determine whether uncomplicated infection becomes sepsis.

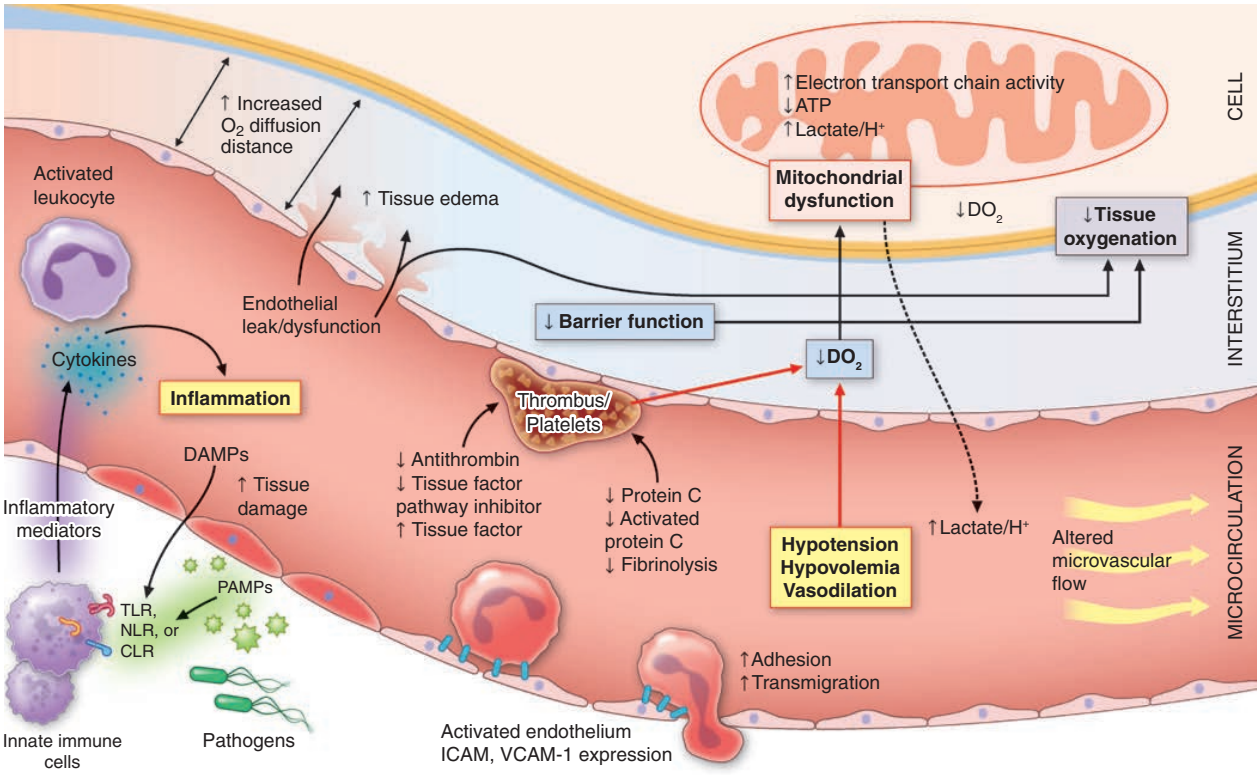

FIGURE 297-1 Select mechanisms implicated in the pathogenesis of sepsis-induced organ and cellular dysfunction. The host response to sepsis involves multiple mechanisms that lead to decreased oxygen delivery (DO_2) at the tissue level. The duration, extent, and direction of these interactions are modified by the organ under threat, host factors (e.g., age, genetic characteristics, medications), and pathogen factors (e.g., microbial load and virulence). The inflammatory response is typically initiated by an interaction between pathogen-associated molecular patterns (PAMPs) expressed by pathogens and pattern recognition receptors expressed by innate immune cells on the cell surface (Toll-like receptors [TLRs] and C-type lectin receptors [CLRs]), in the endosome (TLRs), or in the cytoplasm (retinoic acid inducible gene 1–like receptors and nucleotide-binding oligomerization domain–like receptors [NLRs]). The resulting tissue damage and necrotic cell death lead to release of damage-associated molecular patterns (DAMPs) such as uric acid, high-mobility group protein B1, S100 proteins, and extracellular RNA, DNA, and histones. These molecules promote the activation of leukocytes, leading to greater endothelial dysfunction, expression of intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule 1 (VCAM-1) on the activated endothelium, coagulation activation, and complement activation. This cascade is compounded by macrovascular changes such as vasodilation and hypotension, which are exacerbated by greater endothelial leak tissue edema, and relative intravascular hypovolemia. Subsequent alterations in cellular bioenergetics lead to greater glycolysis (e.g., lactate production), mitochondrial injury, release of reactive oxygen species, and greater organ dysfunction.

Initiation of Inflammation Over the past decade, our knowledge of pathogen recognition has increased tremendously. Pathogens activate immune cells by an interaction with pattern recognition receptors (Fig. 297-1), of which four main classes are prominent: Toll-like receptors (TLRs), RIG-I-like receptors, C-type lectin receptors, and NOD-like receptors; the activity of the last group occurs partially in protein complexes called *inflammasomes*. The recognition of structures conserved across microbial species—so-called pathogen-associated molecular patterns (PAMPs)—by all these receptors results in upregulation of inflammatory gene transcription and initiation of innate immunity. A common PAMP is the lipid A moiety of lipopolysaccharide (LPS or endotoxin), which attaches to the LPS-binding protein on the surface of monocytes, macrophages, and neutrophils. LPS is transferred to and signals via TLR4 to produce and release cytokines such as tumor necrosis factor that grow the signal and alert other cells and tissues. Up to 10 TLRs have been identified in humans.

At the same time, these receptors also sense endogenous molecules released from injured cells—so-called damage-associated molecular patterns (DAMPs), such as high-mobility group protein B1, S100 proteins, and extracellular RNA, DNA, and histones. The release of DAMPs during sterile injuries such as those incurred during trauma gives rise to the concept that the pathogenesis of multiple-organ failure may be similar in sepsis and noninfectious critical illness. In addition to activating the proinflammatory cytokines, the inflammatory responses implicated in the pathogenesis of sepsis also activate the complement system, platelet-activating factor, arachidonic acid metabolites, and nitric oxide.

Coagulation Abnormalities Sepsis is commonly associated with coagulation disorders and frequently leads to disseminated intravascular coagulation. Abnormalities in coagulation are thought to isolate invading microorganisms and/or to prevent the spread of infection and inflammation to other tissues and organs. Excess fibrin deposition is driven by coagulation via tissue factor, a transmembrane glycoprotein expressed by various cell types; by impaired anticoagulant mechanisms, including the protein C system and antithrombin; and by compromised fibrin removal due to depression of the fibrinolytic system. Coagulation (and other) proteases further enhance inflammation via protease-activated receptors. In infections with endothelial predominance (e.g., meningococcemia), these mechanisms can be common and deadly.

Organ Dysfunction Although the mechanisms that underlie organ failure in sepsis are only partially known, impaired tissue oxygenation plays a key role. Several factors contribute to reduced oxygen delivery in sepsis and septic shock, including hypotension, reduced red-cell deformability, and microvascular thrombosis. Inflammation can cause dysfunction of the vascular endothelium, accompanied by cell death and loss of barrier integrity, giving rise to subcutaneous and body-cavity edema. An excessive and uncontrolled release of nitric oxide causes vasomotor collapse, opening of arteriovenous shunts, and pathologic shunting of oxygenated blood from susceptible tissues. In addition, mitochondrial damage due to oxidative stress and other mechanisms impairs cellular oxygen utilization. The slowing of oxidative metabolism, in parallel with impaired oxygen delivery, reduces cellular O_2 extraction. Yet energy (i.e., ATP) is still needed to support basal, vital cellular function, which derives from glycolysis and fermentation and thus yields H^+ and lactate. With severe or prolonged insult, ATP levels fall beneath a critical threshold, bioenergetic failure

ensues, toxic reactive oxygen species are released, and apoptosis leads to irreversible cell death and organ failure. The actual morphologic changes in sepsis-induced organ failure are also complex. Generally, organs such as the lung undergo extensive microscopic changes, while other organs may undergo rather few histologic changes. In fact, some organs (e.g., the kidney) may lack significant structural damage while still having significant tubular-cell changes that impair function.

Anti-Inflammatory Mechanisms The immune system harbors humoral, cellular, and neural mechanisms that may exacerbate the potentially harmful effects of the proinflammatory response. Phagocytes can switch to an anti-inflammatory phenotype that promotes tissue repair, while regulatory T cells and myeloid-derived suppressor cells further reduce inflammation. The so-called neuroinflammatory reflex may also contribute: sensory input is relayed through the afferent vagus nerve to the brainstem, from which the efferent vagus nerve activates the splenic nerve in the celiac plexus, with consequent norepinephrine release in the spleen and acetylcholine secretion by a subset of CD4+ T cells. The acetylcholine release targets α7 cholinergic receptors on macrophages, reducing proinflammatory cytokine release. Disruption of this neural-based system by vagotomy renders animals more vulnerable to endotoxin shock, while stimulation of the efferent vagus nerve or α7 cholinergic receptors attenuates systemic inflammation in experimental sepsis.

Immune Suppression Patients who survive early sepsis but remain dependent on intensive care occasionally demonstrate evidence of a suppressed immune system. These patients may have ongoing infectious foci despite antimicrobial therapy or may experience the reactivation of latent viruses. Multiple investigations have documented reduced responsiveness of blood leukocytes to pathogens in patients with sepsis; these findings were recently corroborated by post-mortem studies revealing strong functional impairments of splenocytes harvested from ICU patients who died of sepsis. Immune suppression was evident in the lungs as well as the spleen; in both organs, the expression of ligands for T cell–inhibitory receptors on parenchymal cells was increased. Enhanced apoptotic cell death, especially of B cells, CD4+ T cells, and follicular dendritic cells, has been implicated in sepsis-associated immune suppression and death. In a cohort of >1000 ICU admissions for sepsis, secondary infections developed in 14% of patients, and the associated genomic response at the time of infection was consistent with immune suppression, including impaired glycolysis and cellular gluconeogenesis. The most common secondary infections included catheter-related bloodstream infections, ventilator-associated infections, and abdominal infections. What is not yet understood is the optimal way to identify those sepsis patients who have hyperinflamed rather than immunosuppressed phenotypes. Similarly, it is unknown whether the dysfunctional immune system is driving organ dysfunction and secondary infections or whether the immune system itself is just another dysfunctional organ.

APPROACH TO THE PATIENT

Sepsis and Septic Shock

At the bedside, a clinician begins by asking, "Is this patient septic?" Consensus criteria for sepsis and septic shock agree on core diagnostic elements, including suspected or documented infection accompanied by acute, life-threatening organ dysfunction. If infection is documented, the clinician must determine the inciting cause and the severity of organ dysfunction, usually by asking: "What just happened?" Severe infection can be evident, but it is often quite difficult to recognize. Many infection-specific biomarkers and molecular diagnostics are under study to help discriminate sterile inflammation from infection, but these tools are not commonly used. The clinician's acumen is still crucial to the diagnosis of infection. Next, the primary physiologic manifestations of organ dysfunction can be assessed quickly at the bedside with a six-organ framework, yielding the SOFA score. Particular focus should then be placed on the presence or absence of shock, which constitutes a clinical emergency. The general manifestations of shock include arterial hypotension with evidence of tissue hypoperfusion (e.g., oliguria, altered mental status, poor peripheral perfusion, or hyperlactemia).

CLINICAL MANIFESTATIONS

The specific clinical manifestations of sepsis are quite variable, depending on the initial site of infection, the offending pathogen, the pattern of acute organ dysfunction, the underlying health of the patient, and the delay before initiation of treatment. The signs of both infection and organ dysfunction may be subtle. Guidelines provide a long list of potential warning signs of incipient sepsis (Table 297-1). Once sepsis has been established and the inciting infection is assumed to be under control, the temperature and white blood cell (WBC) count often return to normal. However, organ dysfunction typically persists.

Cardiorespiratory Failure Two of the most commonly affected organ systems in sepsis are the respiratory and cardiovascular systems. Respiratory compromise classically manifests as acute respiratory distress syndrome (ARDS), defined as hypoxemia and bilateral infiltrates of noncardiac origin that arise within 7 days of the suspected infection. ARDS can be classified by Berlin criteria as mild (PaO_2/FiO_2, 201–300 mmHg), moderate (101–200 mmHg), or severe (≤100 mmHg). A common competing diagnosis is hydrostatic edema secondary to cardiac failure or volume overload. Although traditionally identified by elevated pulmonary capillary wedge measurements from a pulmonary artery catheter (>18 mmHg), cardiac failure can be objectively evaluated on the basis of clinical judgment or focused echocardiography.

Cardiovascular compromise typically presents as hypotension. The cause can be frank hypovolemia, maldistribution of blood flow and intravascular volume due to diffuse capillary leakage, reduced systemic vascular resistance, or depressed myocardial function. After adequate volume expansion, hypotension frequently persists, requiring the use of vasopressors. In early shock, when volume status is reduced, systemic vascular resistance may be quite high with low cardiac output; after volume repletion, however, this picture may rapidly change to low systemic vascular resistance and high cardiac output.

Kidney Injury Acute kidney injury (AKI) is documented in >50% of septic patients, increasing the risk of in-hospital death by six- to eightfold. AKI manifests as oliguria, azotemia, and rising serum creatinine levels and frequently requires dialysis. The mechanisms of sepsis-induced AKI are incompletely understood. AKI may occur in up to 25% of patients in the absence of overt hypotension. Current mechanistic work suggests that a combination of diffuse microcirculatory blood-flow abnormalities, inflammation, and cellular bioenergetic responses to injury contribute to sepsis-induced AKI beyond just organ ischemia.

Neurologic Complications Typical central nervous system dysfunction presents as coma or delirium. Imaging studies typically show no focal lesions, and electroencephalographic findings are usually consistent with nonfocal encephalopathy. Sepsis-associated delirium is considered a diffuse cerebral dysfunction caused by the inflammatory response to infection without evidence of a primary central nervous system infection. Consensus guidelines recommend delirium screening with valid and reliable tools such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Critical-illness polyneuropathy and myopathy are also common, especially in patients with a prolonged course. For survivors of sepsis, neurologic complications can be severe. In a national (U.S.) representative prospective cohort of >1000 elderly patients with severe sepsis, moderate to severe cognitive impairment increased by 10.6 percentage points among patients who survived severe sepsis (odds ratio, 3.34; 95% confidence interval [CI], 1.53–7.25) over that among survivors of nonsepsis hospitalizations. Many of these limitations persisted for up to 8 years.

Additional Manifestations Many other abnormalities occur in sepsis, including ileus, elevated aminotransferase levels, altered glycemic control, thrombocytopenia and disseminated intravascular coagulation, adrenal dysfunction, and sick euthyroid syndrome. Adrenal

dysfunction in sepsis is widely studied and is thought to be related more to reversible dysfunction of the hypothalamic–pituitary axis or tissue glucocorticoid resistance than to direct damage to the adrenal gland. The diagnosis is difficult to establish. Recent clinical practice guidelines do not recommend use of the adrenocorticotropic hormone stimulation test or determination of the plasma cortisol level to detect relative glucocorticoid insufficiency.

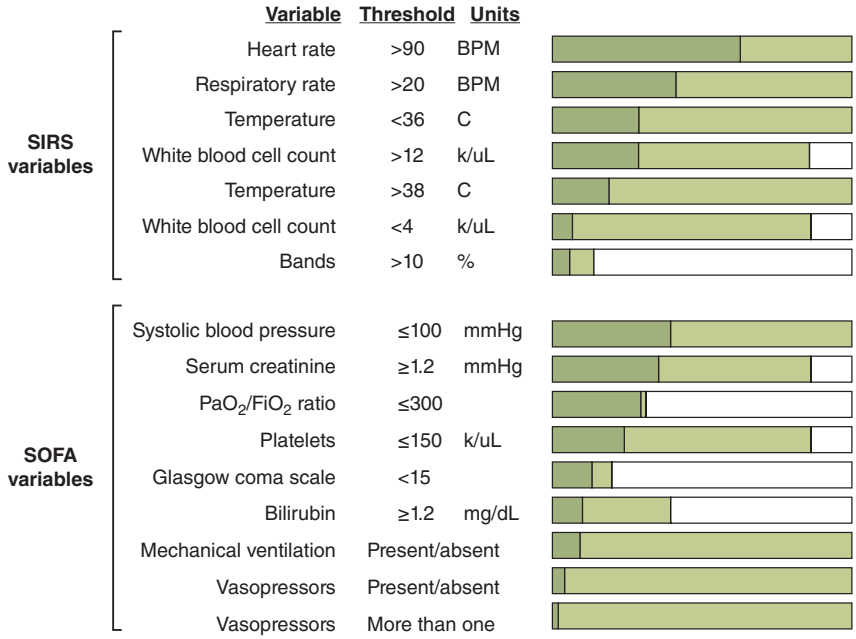

FIGURE 297-2 Distribution of SIRS and SOFA variables among infected patients at risk for sepsis, as documented in the electronic health record. Dark green bars represent the proportion of such patients with abnormal findings; light green bars, the proportion with normal findings; and white bars, the proportion with missing data. *(Adapted from CW Seymour et al: Assessment of clinical criteria for sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock [Sepsis-3]. JAMA 315:762, 2016.)*

DIAGNOSIS

Laboratory and Physiologic Findings

A variety of laboratory and physiologic changes are found in patients with suspected infection who are at risk for sepsis. In a 12-hospital cohort of electronic health records related to >70,000 encounters (Fig. 297-2), only tachycardia (heart rate, >90 beats per min) was present in >50% of encounters; the most common accompanying abnormalities were tachypnea (respiratory rate, >20 breaths per min), hypotension (systolic blood pressure, ≤100 mmHg), and hypoxia (SaO_2, ≤90%). Leukocytosis (WBC count, >12,000/μL) was present in fewer than one-third of patients and leukopenia (WBC count, <4000/μL) in fewer than 5%. Notably, many features that may identify acute organ dysfunction, such as platelet count, total bilirubin, or serum lactate level, are measured in only a small minority of at-risk encounters. If measured, metabolic acidosis with anion gap may be detected, as respiratory muscle fatigue occurs in sepsis-associated respiratory failure. Other, less common findings include serum hypoalbuminemia, troponin elevation, hypoglycemia, and hypofibrinogenemia.

Diagnostic Criteria There is no specific test for sepsis, nor is there a gold-standard method for determining whether a patient is septic. In fact, the definition of sepsis can be written as a logic statement:

sepsis = f (threat to life | organ dysfunction | dysregulated host response | infection),

where sepsis is the dependent variable, which in turn is a function of four independent variables linked in a causal pathway, with—from left to right—one conditional upon the other. There may be uncertainty about whether each variable exists, whether it can be measured, and whether the causal and conditional relationships hold. If we assume that organ dysfunction exists and can be measured, then attributing the marginal degradation in function to a dysregulated host response is not simple and requires the ability to determine preexisting dysfunction, other noninfectious contributions to organ dysfunction, and—ideally—the mechanism by which the host response to an infection causes organ dysfunction.

In order to sort through these complex details, clinicians need simple bedside criteria to operationalize the logic statement (Fig. 297-3). With this mandate, the Sepsis Definitions Task Force recommended that, once infection is suspected, clinicians consider whether it has caused organ dysfunction by determining a SOFA score. The SOFA score ranges from 0 to 24 points, with up to 4 points accrued across six organ systems. The SOFA score is widely studied in the ICU among patients with infection, sepsis, and shock. With ≥2 new SOFA points, the infected patient is considered septic and may be at ≥10% risk of in-hospital death.

Because the SOFA score requires multiple laboratory tests and may be costly to measure repeatedly, the quick SOFA (qSOFA) score was proposed as a clinical prompt to identify patients at high risk of sepsis outside the ICU, whether on the medical ward or in the emergency department. The qSOFA score ranges from 0 to 3 points, with 1 point each for systolic hypotension (≤100 mmHg), tachypnea (≥22 breaths/min), or altered mentation. A qSOFA score of ≥2 points has a predictive value for sepsis similar to that of more complicated measures of organ dysfunction. The qSOFA score is undergoing broader evaluation in other cohorts, in low-and middle-income settings, and in algorithms linked to clinical decision-making. Recent work has also shown that, although SIRS criteria may be fulfilled in sepsis, they sometimes are not and do not meaningfully contribute to the identification of patients with suspected infection who are at greater risk of a poor course, ICU admission, or death—outcomes more common among patients with sepsis than among those without.

As stated above, recent definitions have specified that septic shock is a subset of sepsis in which circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality risk, but the application of this definition as a criterion for enrollment of patients varies significantly in clinical trials, observational studies, and quality improvement work. For clarity, criteria are proposed for septic shock that include (1) sepsis plus (2) the need for vasopressor therapy to elevate mean arterial pressure to ≥65 mmHg, with (3) a serum lactate concentration >2.0 mmol/L after adequate fluid resuscitation.

The new definitions and diagnostic criteria were externally validated in >1 million encounters stored in electronic health records. Nevertheless, given the uncertainty around the diagnosis of sepsis, Sepsis-3 is undergoing both validation in prospective studies and incorporation into clinical practice and quality improvement initiatives.

Arterial lactate is a long-studied marker of tissue hypoperfusion, and hyperlactemia and delayed lactate clearance are associated with a greater incidence of organ failure and death in sepsis. In a study of >1200 patients with suspected infection, 262 (24%) of 1081 patients exhibited an elevated lactate concentration (≥2.5 mmol/L) even in the setting of normal systolic blood pressure (>90 mmHg) and were at elevated risk of 28-day in-hospital mortality. However, lactic acidosis may occur in the presence of alcohol intoxication, liver disease, diabetes mellitus, administration of total parenteral nutrition, or antiretroviral treatment, among other conditions. Furthermore, in sepsis, an elevated lactate concentration may simply be the manifestation of impaired clearance. These factors may confound the use of lactate as a stand-alone biomarker for the diagnosis of sepsis; thus it should be used in the context of other markers of infection and organ dysfunction.

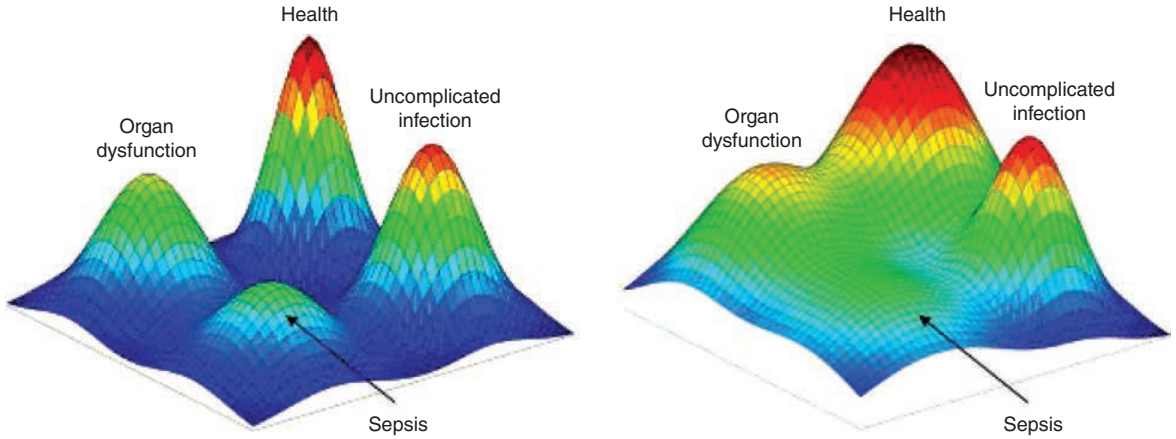

FIGURE 297-3 Schematic of the importance of accurate, easy-to-use criteria for sepsis and its components, infection and organ dysfunction. In the ideal case (*left*), criteria clearly distinguish sepsis patients from other patients with uncomplicated infection or organ dysfunction. The reality (*right*), however, is that existing criteria fail to make clear distinctions, leaving a significant proportion of patients in areas of uncertainty. *(Adapted from DC Angus et al: A framework for the development and interpretation of different sepsis definitions and clinical criteria. Crit Care Med 44:e113, 2016.)*

TREATMENT

Sepsis and Septic Shock

EARLY TREATMENT OF SEPSIS AND SEPTIC SHOCK

Recommendations for sepsis care begin with prompt diagnosis. Recognition of septic shock by a clinician constitutes an emergency in which immediate treatment can be life-saving. Up-to-date guidelines for treatment are derived from international clinical practice guidelines provided by the Surviving Sepsis Campaign. This consortium of critical care, infectious disease, and emergency medicine professional societies has issued three iterations of clinical guidelines for the management of patients with sepsis and septic shock **(Table 297-2)**.

The initial management of infection requires several steps: forming a probable diagnosis, obtaining samples for culture, initiating empirical antimicrobial therapy, and achieving source control. More than 30% of patients with severe sepsis require source control, mainly for abdominal, urinary, and soft-tissue infections. The mortality rate is lower among patients with source control than among those without, although the timing of intervention is debated. For empirical antibiotic therapy **(Table 297-3)**, the appropriate choice depends on the suspected site of infection, the location of infection onset (i.e., the community, a nursing home, or a hospital), the patient's medical history, and local microbial susceptibility patterns. In a single-center study of >2000 patients with bacteremia, the number of patients who needed to receive appropriate antimicrobial therapy in order to prevent one patient death was 4.0 (95% CI, 3.7–4.3).

Antibiotic delays may be deadly. For every 1-h delay among patients with sepsis, a 3–7% increase in the odds of in-hospital death is reported. Although meta-analyses report conflicting results, international clinical practice guidelines recommend the administration of appropriate broad-spectrum antibiotics within 1 h of recognition of severe sepsis or septic shock. Empirical antifungal therapy should be administered only to septic patients at high risk for invasive candidiasis.

The treatment elements listed above form the basis for two "bundles" of care: an initial management bundle to be completed within 3 h of presentation and a management bundle to be completed within 6 h. The initial management bundle includes (1) early administration of appropriate broad-spectrum antibiotics, (2) collection of blood for culture before antibiotic administration, and (3) measurement of serum lactate levels. The management bundle includes (1) an intravenous fluid bolus, (2) treatment with vasopressors for persistent hypotension or shock, and (3) re-measurement of serum lactate levels. Implementation of these two bundles has been associated with improved outcome in large multinational studies.

Other elements of the initial management bundle are cardiorespiratory resuscitation and mitigation of the immediate threats of uncontrolled infection. Early resuscitation requires a structured approach including the administration of IV fluids and vasopressors, with oxygen therapy and mechanical ventilation to support injured organs. The exact components required to optimize resuscitation, such as choice and amount of fluid, appropriate type and intensity of hemodynamic monitoring, and role of adjunctive vasoactive agents, all remain controversial, even after the completion and reporting of recent large randomized trials.

Evidence from an older study suggests that protocol-based, early goal-directed therapy (EGDT) may confer a greater survival advantage than clinical assessments of organ perfusion and management without a protocol. EGDT included an aggressive resuscitation protocol with specific hemodynamic thresholds for fluid administration, blood transfusion, and use of ionotropes. Given the many controversial features of this older single-center trial, the recent ProCESS trial compared protocol-based standard care with protocol-based EGDT and usual care in >31 emergency departments in the United States. Among 1341 patients, the 60-day in-hospital mortality rate for protocol-based standard care (18.2%) was similar to that for usual care (18.9%) and protocol-based EGDT (21%). The ARISE trial confirmed this finding, showing that, among 1600 patients with early septic shock at 51 centers in Australia and New Zealand, 90-day mortality was similar for EGDT and usual care. Finally, the ProMISe trial, which enrolled 1260 patients in 56 hospitals in England, found that EGDT offered no mortality benefit in early septic shock but did increase treatment intensity and cost. Multiple subsequent meta-analyses of the ProCESS, ARISE, and ProMISe trials confirmed that EGDT offers no mortality benefit while increasing health care utilization and ICU admission in well-resourced countries. Modified versions of EGDT were also tested in lower-resourced settings, with no change in outcome. Thus EGDT is no longer recommended as the primary strategy for early resuscitation in septic shock. Nonetheless, some form of resuscitation is considered essential, and a standardized approach, akin to the use of "trauma teams," has been advocated to ensure prompt care. The patient should be moved to an appropriate setting, such as the ICU, for ongoing care.

SUBSEQUENT TREATMENT OF SEPSIS AND SEPTIC SHOCK

After initial resuscitation, attention is focused on monitoring and support of organ function, avoidance of complications, and de-escalation of care when possible.

Monitoring Hemodynamic monitoring devices may clarify the primary physiologic manifestations in sepsis and septic shock. The clinical usefulness of these monitoring devices can be attributable to the device itself, the algorithm linked to the device, or the static/dynamic target of the algorithm. Decades ago, the standard care of shock patients included invasive devices like the pulmonary artery

TABLE 297-2 Elements of Care in Sepsis and Septic Shock: Recommendations Adapted from International Consensus Guidelines

Resuscitation
Sepsis and septic shock constitute an emergency, and treatment should begin right away.
Resuscitation with IV crystalloid fluid (30 mL/kg) should begin within the first 3 h.
Saline or balanced crystalloids are suggested for resuscitation.
If the clinical examination does not clearly identify the diagnosis, hemodynamic assessments (e.g., with focused cardiac ultrasound) can be considered.
In patients with elevated serum lactate levels, resuscitation should be guided towards normalizing these levels when possible.
In patients with septic shock requiring vasopressors, the recommended target mean arterial pressure is 65 mmHg.
Hydroxyethyl starches and gelatins are not recommended.
Norepinephrine is recommended as the first-choice vasopressor.
Vasopressin should be used with the intent of reducing the norepinephrine dose.
The use of dopamine should be avoided except in specific situations—e.g., in those patients at highest risk of tachyarrhythmias or relative bradycardia.
Dobutamine use is suggested when patients show persistent evidence of hypoperfusion despite adequate fluid loading and use of vasopressors.
Red blood cell transfusion is recommended only when the hemoglobin concentration decreases to <7.0 g/dL in the absence of acute myocardial infarction, severe hypoxemia, or acute hemorrhage.
Infection Control
So long as no substantial delay is incurred, appropriate samples for microbiologic cultures should be obtained before antimicrobial therapy is started.
IV antibiotics should be initiated as soon as possible (within 1 h); specifically, empirical broad-spectrum therapy should be used to cover all likely pathogens.
Antibiotic therapy should be narrowed once pathogens are identified and their sensitivities determined and/or once clinical improvement is evident.
If needed, source control should be undertaken as soon as is medically and logistically possible.
Daily assessment for de-esclation of antimicrobial therapy should be conducted.
Respiratory Support
A target tidal volume of 6 mL/kg of predicted body weight (compared with 12 mL/kg in adult patients) is recommended in sepsis-induced ARDS.
A higher PEEP rather than a lower PEEP is used in moderate to severe sepsis-induced ARDS.
In severe ARDS (PaO_2/FIO_2, <150 mmHg), prone positioning is recommended, and recruitment maneuvers and/or neuromuscular blocking agents for ≤48 h are suggested.
A conservative fluid strategy should be used in sepsis-induced ARDS if there is no evidence of tissue hypoperfusion.
Routine use of a pulmonary artery catheter is not recommended.
Spontaneous breathing trials should be used in mechanically ventilated patients who are ready for weaning.
General Supportive Care
Patients requiring a vasopressor should have an arterial catheter placed as soon as is practical.
Hydrocortisone is not suggested in septic shock if adequate fluids and vasopressor therapy can restore hemodynamic stability.
Continuous or intermittent sedation should be minimized in mechanically ventilated sepsis patients, with titration targets used whenever possible.
A protocol-based approach to blood glucose management should be used in ICU patients with sepsis, with insulin dosing initiated when two consecutive blood glucose levels are >180 mg/dL.
Continuous or intermittent renal replacement therapy should be used in patients with sepsis and acute kidney injury.
Pharmacologic prophylaxis (unfractionated heparin or low-molecular-weight heparin) against venous thromboembolism should be used in the absence of contraindications.
Stress ulcer prophylaxis should be given to patients with risk factors for gastrointestinal bleeding.
The goals of care and prognosis should be discussed with patients and their families.

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; PEEP, positive end-expiratory pressure.

Source: Adapted from A Rhodes et al: Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med 45:486, 2017.

catheter (PAC), also known as the continuous $ScvO_2$ catheter. The PAC can estimate cardiac output and measure mixed venous oxygen saturation, among other parameters, to refine the etiology of shock and potentially influence patient outcomes. Recently, a Cochrane review of 2923 general-ICU patients (among whom the proportion of patients in shock was not reported) found no difference in mortality with or without PAC management, and the PAC therefore is no longer recommended for routine use. Instead, a variety of noninvasive monitoring tools, such as arterial pulse contour analysis (PCA) or focused echocardiography, can provide continuous estimates of parameters such as cardiac output, beat-to-beat stroke volume, and pulse pressure variation. These tools, along with passive leg-raise maneuvers or inferior vena cava collapsibility on ultrasound, can help determine a patient's volume responsiveness but require that a variety of clinical conditions be met (e.g., patient on mechanical ventilation, sinus rhythm); in addition, more evidence from larger randomized trials on the impact of these tools in daily management is needed.

Support Of Organ Function The primary goal of organ support is to improve delivery of oxygen to the tissues as quickly as possible. Depending on the underlying physiologic disturbance, this step may require administration of IV fluids or vasopressors, blood transfusions, or ventilatory support.

Many crystalloids can be used in septic shock, including 0.9% normal saline, Ringer's lactate, Hartmann's solution, and Plasma-Lyte. Because crystalloid solutions vary in tonicity and inorganic/organic anions, few of these preparations closely resemble plasma. Normal saline is widely used in the United States. Colloid solutions (e.g., albumin, dextran, gelatins, or hydroxyethyl starch) are the most widely used fluids in critically ill patients, with variability across ICUs and countries. A clinician's choice among colloids is influenced by availability, cost, and the desire to minimize interstitial edema. Many think that a greater intravascular volume is gained by use of colloids in shock, but the effects of colloids are modified by molecular weight and concentration as well as by vascular endothelial changes during inflammation. A network meta-analysis using direct and indirect comparisons in sepsis found evidence of higher mortality with starch than with crystalloids (relative risk [RR], 1.13; 95% CI, 0.99–1.30 [high confidence]) and no difference between albumin (RR, 0.83; 95% CI, 0.65, 1.04 [moderate confidence]) or gelatin (RR, 1.24; 95%CI, 0.61, 2.55 [very low confidence]) and crystalloids. In general, crystalloids are recommended on the basis of strong evidence as

TABLE 297-3 Initial Antimicrobial Therapy for Severe Sepsis with No Obvious Source in Adults with Normal Renal Function

CLINICAL CONDITION	ANTIMICROBIAL REGIMENS[a]
Septic shock (immunocompetent adult)	The many acceptable regimens include (1) piperacillin-tazobactam (3.375–4.5 g q6h), (2) cefepime (2 g q12h), or (3) meropenem (1 g q8h) or imipenem-cilastatin (0.5 g q6h). If the patient is allergic to β-lactam antibiotics, use (1) aztreonam (2 g q8h) or (2) ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q24h). Add vancomycin (loading dose of 25–30 mg/kg, then 15–20 mg/kg q8–12h) to each of the above regimens.
Neutropenia (<500 neutrophils/μL)	Regimens include (1) cefepime (2 g q8h), (2) meropenem (1 g q8h) or imipenem-cilastatin (0.5 g q6h) or doripenem (500 mg q8h), or (3) piperacillin-tazobactam (3.375 g q4h). Add vancomycin (as above) if the patient has a suspected central line–associated bloodstream infection, severe mucositis, skin/soft tissue infection, or hypotension. Add tobramycin (5–7 mg/kg q24h) plus vancomycin (as above) plus caspofungin (one dose of 70 mg, then 50 mg q24h) if the patient has severe sepsis/septic shock.
Splenectomy	Use ceftriaxone (2 g q24h, or—in meningitis—2 g q12h). If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin (as above). If the patient is allergic to β-lactam antibiotics, use levofloxacin (750 mg q24h) or moxifloxacin (400 mg q24h) plus vancomycin (as above).

[a]All agents are administered by the intravenous route.

Source: Adapted in part from DN Gilbert et al: *The Sanford Guide to Antimicrobial Therapy*, 47th ed, 2017; and from RS Munford: Sepsis and septic shock, in DL Kasper et al (eds). *Harrison's Principles of Internal Medicine*, 19th ed. New York, McGraw-Hill, 2015, p 1757.

first-line fluids for sepsis resuscitation, with specific caveats; their use is guided by resolution of hypotension, oliguria, altered mentation, and hyperlactemia. Only weak evidence supports the use of balanced crystalloids, and guidelines recommend against using hydroxyethyl starches for intravascular volume replacement.

When circulating fluid volume is adequate, vasopressors are recommended to maintain perfusion of vital organs. Vasopressors such as norepinephrine, epinephrine, dopamine, and phenylephrine differ in terms of half-life, β- and α-adrenergic stimulation, and dosing regimens. Recent evidence comes from the SOAP II trial, a double-blind randomized clinical trial at eight centers comparing norepinephrine with dopamine in 1679 undifferentiated ICU patients with shock, of whom 63% were septic. Although no difference was observed in 28-day mortality or in predefined septic-shock subgroup, arrhythmias were significantly greater with dopamine. These findings were confirmed in a subsequent meta-analysis. As a result, expert opinion and consensus guidelines recommend norepinephrine as the first-choice vasopressor in septic shock. Levels of the endogenous hormone vasopressin may be low in septic shock, and the administration of vasopressin can reduce the norepinephrine dose. Consensus guidelines suggest adding vasopressin (up to 0.03 U/min) in patients without a contraindication to norepinephrine, with the intent of raising mean arterial pressure or decreasing the norepinephrine dose. There may be select indications for use of alternative vasopressors—e.g., when tachyarrhythmias from dopamine or norepinephrine, limb ischemia from vasopressin, or other adverse effects dictate.

The transfusion of red blood cells to high thresholds (>10 g/dL) had been suggested as part of EGDT in septic shock. However, the recent Scandinavian TRISS trial in 1005 septic shock patients demonstrated that a lower threshold (7 g/dL) resulted in 90-day mortality rates similar to those with a higher threshold (9 g/dL) and reduced transfusions by almost 50%.

Significant hypoxemia (PaO_2, <60 mmHg; or SaO_2, <90%), hypoventilation (rising $PaCO_2$), increased work of breathing, and inadequate or unsustainable compensation for metabolic acidosis (pH <7.20) are common indications for mechanical ventilatory support. Endotracheal intubation protects the airway, and positive-pressure breathing allows oxygen delivery to metabolically active organs in favor of inspiratory muscles of breathing and the diaphragm. An experiment in dogs showed that the relative proportion of cardiac output delivered to respiratory muscles in endotoxic shock decreased by fourfold with spontaneous ventilation over that with mechanical ventilation. During intubation, patients in shock should be closely monitored for vasodilatory effects of sedating medications or compromised cardiac output due to increased intrathoracic pressure, both of which may cause hemodynamic collapse. With hemodynamic instability, noninvasive mask ventilation may be less suitable in patients experiencing sepsis-associated acute respiratory failure.

Adjuncts One of the great disappointments in sepsis management over the past 30 years has been the failure to convert advances in our understanding of the underlying biology into new therapies. Researchers have tested both highly specific agents and those with more pleotropic effects. The specific agents can be divided into those designed to interrupt the initial cytokine cascade (e.g., anti-LPS or anti-proinflammatory cytokine strategies) and those that interfere with dysregulated coagulation (e.g., antithrombin or activated protein C). Recombinant activated protein C (aPC) was one of the first agents approved by the U.S. Food and Drug Administration and was the most widely used. A large, randomized, double-blind, placebo-controlled, multicenter trial of aPC in severe sepsis (the PROWESS trial) was reported in 2001; the data suggested an absolute risk reduction of up to 6% among aPC-treated patients with severe sepsis. However, subsequent phase 3 trials failed to confirm this effect, and the drug was withdrawn from the market. It is no longer recommended in the care of sepsis or septic shock.

Many adjunctive treatments in sepsis and septic shock target changes in the innate immune response and coagulation cascade. Specific adjuncts like glucocorticoids in septic shock have continued to be widely used. A large negative clinical trial and a conflicting systematic review in 2009 extended the debate about whether glucocorticoids lower 28-day mortality or improve shock reversal. Most meta-analyses report no change in mortality but an increase in shock reversal with glucocorticoid treatment. The recent HYPRESS trial found no difference between patients with severe sepsis who were treated with glucocorticoids and control patients in terms of the development of shock or the mortality rate. These data and others led to a suggestion in international clinical practice guidelines against using IV hydrocortisone to treat septic shock if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If not, the guidelines suggest the administration of IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

Among other adjuncts, IV immunoglobulin may be associated with potential benefit, but significant questions remain and such treatment is not part of routine practice. Despite a large number of observational studies suggesting that statin use mitigates the incidence or outcome of sepsis and severe infection, there are no confirmatory randomized controlled trials, and statins are not an element in routine sepsis care.

De-Escalation of Care Once patients with sepsis and septic shock are stabilized, it is important to consider which therapies are no longer required and how care can be minimized. The de-escalation of initial broad-spectrum therapy, which observational evidence indicates is safe, may reduce the emergence of resistant organisms as well as potential drug toxicity and costs. The added value of combination antimicrobial therapy over that of adequate single-agent antibiotic therapy in severe sepsis has not been established. Current guidelines recommend combination antimicrobial therapy only for neutropenic sepsis and sepsis caused by *Pseudomonas*. Large trials are under way in the United States to determine how serum biomarkers like procalcitonin can assist clinicians in minimizing antibiotic exposure, while European trials are indicating that this

biomarker may lead to a reduction in the duration of treatment and in daily defined doses in critically ill patients with a presumed bacterial infection.

PROGNOSIS

Before modern intensive care, sepsis and septic shock were highly lethal, with infection leading to compromise of vital organs. Even with intensive care, nosocomial mortality rates for septic shock often exceeded 80% as recently as 30 years ago. Now, the U.S. Burden of Disease Collaborators report that the primary risk factor for sepsis and septic shock—i.e., infection—is the fifth leading cause of years of productive life lost because of premature death. More than half of sepsis cases require ICU admission, representing 10% of all ICU admissions. However, with advances in training, surveillance, monitoring, and prompt initiation of supportive care for organ dysfunction, the mortality rate from sepsis and septic shock is now closer to 20% in many series. Although some data suggest that mortality trends are even lower, attention has been focused on the trajectory of recovery among survivors. Patients who survive to hospital discharge after sepsis remain at increased risk of death in the following months and years. Those who survive often suffer from impaired physical or neurocognitive dysfunction, mood disorders, and low quality of life. In many studies, it is difficult to determine the causal role of sepsis. However, an analysis of the Health and Retirement Study—a large longitudinal cohort study of aging Americans—suggested that severe sepsis significantly accelerated physical and neurocognitive decline. Among survivors, the rate of hospital readmission within 90 days after sepsis exceeds 40%.

PREVENTION

In light of the persistently high mortality risk in sepsis and septic shock, prevention may be the best approach to reducing avoidable deaths, but preventing sepsis is a challenge. The aging of the population, the overuse of inappropriate antibiotics, the rising incidence of resistant microorganisms, and the use of indwelling devices and catheters contribute to a steady burden of sepsis cases. The number of cases could be reduced by avoiding unnecessary antibiotic use, limiting use of indwelling devices and catheters, minimizing immune suppression when it is not needed, and increasing adherence to infection control programs at hospitals and clinics. To facilitate earlier treatment, such pragmatic work could be complemented by research into the earliest pathophysiology of infection, even when symptoms of sepsis are nascent. In parallel, the field of implementation science could inform how best to increase adoption of infection control in high-risk settings and could guide appropriate care.

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298 Cardiogenic Shock and Pulmonary Edema

David H. Ingbar, Holger Thiele

Cardiogenic shock (CS) and pulmonary edema are life-threatening high acuity conditions that require treatment as medical emergencies, usually in an intensive care unit (ICU) or cardiac intensive care unit (CICU). The most common joint etiology is severe left ventricular (LV) dysfunction from myocardial infarction (MI) that leads to pulmonary congestion and/or systemic hypoperfusion **(Fig. 298-1)**. **The pathophysiology of pulmonary edema and shock are discussed in Chaps. 33 and 296, respectively.**

CARDIOGENIC SHOCK

CS is a low cardiac output state resulting in life-threatening end-organ hypoperfusion and hypoxia. The clinical presentation is typically characterized by persistent hypotension (<90 mmHg systolic blood pressure [BP]) unresponsive to volume replacement and is accompanied by clinical features of peripheral hypoperfusion, such as elevated arterial lactate (>2 mmol/L). Objective hemodynamic parameters such as cardiac index or pulmonary capillary wedge pressure can help confirm the diagnosis, but are not mandatory. The in-hospital mortality rates range from 40 to 60%, depending on shock severity and the associated underlying cause. Acute MI with LV dysfunction remains the most frequent cause of CS with other causes listed in **Table 298-1**. Circulatory failure based on cardiac dysfunction may be caused by primary myocardial failure, most commonly secondary to acute MI **(Chap. 269)**, and less frequently by cardiomyopathy or myocarditis **(Chap. 254)**, cardiac tamponade **(Chap. 265)**, arrhythmias **(Chap. 249)**, or critical valvular heart disease **(Chap. 256)**.

Incidence The incidence of CS complicating acute MI has decreased to 5–10%, largely due to increasing use of early mechanical reperfusion therapy for acute MI. Shock is more common with ST-elevation MI (STEMI) than with non-STEMI **(Chap. 269)**.

LV failure accounts for ~80% of cases of CS complicating acute MI. Acute severe mitral regurgitation (MR), ventricular septal rupture (VSR), predominant right ventricular (RV) failure, and free wall rupture or tamponade account for the remainder. A recently recognized uncommon cause of transient CS is the Takotsubo syndrome.

Pathophysiology The understanding of the complex pathophysiology of CS has evolved over the past decades. In general, a profound depression of myocardial contractility results in a deleterious spiral of reduced cardiac output, low blood pressure, and ongoing myocardial ischemia, followed by further contractility reduction (Fig. 298-1). This vicious cycle usually leads to death if not interrupted. CS can result in both acute and subacute derangements to the entire circulatory system. Hypoperfusion of vital organs and extremities remains a clinical hallmark. Although ineffective stroke volume is the inciting event, inadequate circulatory compensation also may contribute to shock. Initial peripheral vasoconstriction may improve coronary and peripheral perfusion at the cost of increased afterload. However, over the course of CS systemic inflammation response triggered by acute cardiac injury often induces pathologic vasodilatation. Inflammatory cytokines, endothelial and inducible nitric oxide synthase may augment NO production, accompanied by peroxynitrite, which has a negative inotropic effect and is cardiotoxic. Lactic acidosis and hypoxemia contribute to the vicious circle, as severe acidosis reduces the efficacy of endogenous and exogenous catecholamines. During ICU support bleeding and/or