

Approach to the Patient with Sepsis

Jason B. Martin, MD^a, Arthur P. Wheeler, MD^{a,b,*}

KEYWORDS

• Sepsis • Septic shock • Definitions • Management

Sepsis syndrome results from a host reaction to infection, which includes a robust systemic inflammatory response, enhanced coagulation, and impaired fibrinolysis.¹ The relationships among infection, inflammation, and sepsis are well described in professional society consensus statements.² The systemic inflammatory response syndrome (SIRS) is defined by the constellation of fever or hypothermia, tachycardia, tachypnea, and leukocytosis, leukopenia, or the presence of immature neutrophils **Table 1**. SIRS can result from numerous conditions but only becomes “sepsis” when infection is etiologic. When sepsis causes at least one organ dysfunction, the syndrome is termed “severe sepsis,” and sepsis-induced hypotension that is refractory to fluid challenge defines “septic shock.”

While the SIRS criteria are sensitive for septic patients, they are criticized for lacking specificity. Many, if not most, ICU patients have tachypnea and tachycardia, raising doubt as to the diagnostic utility of the SIRS criteria.³ Although the specificity of SIRS is increased by requiring three of the criteria, or by mandating that one of two required criteria be abnormal temperature or white blood cell count, even two criteria maintain prognostic importance.⁴

EPIDEMIOLOGY AND OUTCOMES

Large epidemiologic studies report an incidence of 1 to 3 cases per 1000 population per year⁵ resulting in approximately 750,000 cases annually in the United States. The average sepsis survivor

requires 7 to 14 days of intensive care unit (ICU) support with much of this time spent on a ventilator. After ICU discharge, an additional 10- to 14-day hospital stay is typical. Thus, the average hospital length of stay for survivors is 3 to 5 weeks. Hospital charges in excess of tens of thousands of dollars are common for individual patients, resulting in annual US expenditures of nearly \$17 billion.^{6,7}

Septic patients present typically in their sixth or seventh decade of life,^{6,8,9} and the average age of afflicted patients has increased consistently over time.^{5,10} For unclear reasons, males are affected more commonly.⁶ Although the condition can occur in previously healthy individuals, it is more common in patients with chronic diseases, particularly the immunocompromised. Occurrence rates are higher in those with diabetes mellitus, malignancy, chronic immune suppressive therapy, or human immunodeficiency virus infection. Patients with disrupted skin, especially trauma victims or surgical patients, are also more likely to develop severe sepsis. In the United States, African Americans have higher rates of hospitalization and mortality from sepsis as compared with whites, but the rates of case fatality are similar between the two groups.¹¹ Despite these observations, sepsis has no definitive age, gender, racial, or geographic boundaries.

Today hospital mortality rates remain unacceptably high; 30% to 40% of patients die despite prompt, comprehensive treatment. Predictors of worse outcomes include advanced age,¹⁰ cancer,^{12,13} and a hypothermic presentation.¹⁴

^a Division of Allergy, Pulmonary & Critical Care, Vanderbilt University Medical Center, 1161 21st Avenue South, Suite T-1210 MCN, Nashville, TN 37232-2650, USA

^b Medical Intensive Care Unit, Vanderbilt University Medical Center, 1161 21st Avenue South, Suite T-1210 MCN, Nashville, TN 37232-2650, USA

* Corresponding author. Division of Allergy, Pulmonary & Critical Care, Vanderbilt University Medical Center, 1161 21st Avenue South, Suite T-1210 MCN, Nashville, TN 37232-2650.

E-mail address: art.wheeler@vanderbilt.edu (A.P. Wheeler).

Term	Definition and Criteria
Infection	Microorganism invasion of a normally sterile site
Bacteremia	Presence of viable microorganisms in the blood
Systemic Inflammatory Response Syndrome (SIRS)	A systemic inflammatory response to a pathologic insult, such as a burn, trauma, pancreatitis, or infection. SIRS requires two or more of the following conditions: <ul style="list-style-type: none"> • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO₂ <32 mm Hg • WBC >12,000/mm³, <4000 cells/mm³, or >10% immature (band) forms
Sepsis (= 1 + 3)	The syndrome caused by a systemic inflammatory response secondary to infection
Severe sepsis	Sepsis associated with organ dysfunction. Specific organ dysfunctions include, but are not limited to, hypotension, renal dysfunction, respiratory failure, and altered mental status.
Septic shock (= 5 + 7)	Sepsis with hypotension or hypoperfusion despite adequate fluid resuscitation.
Hypotension, sepsis-induced	A decrease in systolic blood pressure <90 mm Hg, a mean arterial pressure <60 mm Hg, or a reduction of >40 mm Hg from baseline

Data from Bone RC, Balk RA, Cerra FB, et al. American-College of Chest Physicians Society of Critical Care Medicine Consensus Conference—definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20(6):864–74.

Historically, it was believed specific characteristics of the invading pathogen determined prognosis, but recent investigations have undermined this long-held belief.^{15–17} The identity of the infecting organism is of lesser consequence than physiologic derangements provided appropriate, prompt antimicrobial therapy is administered. At the bedside, the best practical predictor of outcome is simply the number of organ systems with sepsis-induced dysfunction.^{4,18} Each new organ system failure adds roughly 15% to 20% risk of death to the baseline 10% to 15% mortality rate seen among ICU patients.⁵ On average, patients have two or three failing organ systems at the time of diagnosis.^{18,19}

In addition to the number of malfunctioning organs, the severity of organ dysfunction also correlates with outcome.^{5,20,21} For example, the need for higher or escalating vasoactive medication doses is associated with a worse prognosis than lower dose requirements or no requirement at all.¹⁸ Likewise, increasing levels of renal dysfunction, as measured by either the Risk/Injury/Failure/Loss/End-Stage Renal Disease (RIFLE) or Acute Kidney Injury Network (AKIN) criteria, are also prognostic, including degrees of creatinine elevation heretofore thought to be unimportant.^{22,23} Several severity of illness scores have been developed based on assessment of organ functions,

including the Acute Physiologic and Chronic Health Evaluation (APACHE) system and the Sequential Organ Failure Assessment (SOFA). These scoring systems are best used as tools to compare severity of illness in large study populations and have less utility as prognostic tools for individual patients.²⁴

PRESENTATION AND DIAGNOSIS

Sepsis is diagnosed by history and physical findings, corroborated by laboratory data such as circulating leukocyte count, body fluid examination, and culture. Detecting the syndrome in hospitalized patients is particularly important, as nosocomial sepsis is associated with longer lengths of stay and higher mortality rates as compared with community-acquired sepsis.^{25,26} Although there is occasionally some degree of uncertainty, recognition of sepsis usually is not difficult. Most patients will meet at least three SIRS criteria at ICU admission.²⁷ Minute ventilation is almost always increased, and tachypnea is present in up to 80% of ICU patients. Fever occurs in approximately 60% of patients at admission²⁷ but may be suppressed in those with advanced age, renal failure, or patients taking anti-inflammatory medications.^{14,28} Hypothermia, although uncommon, is an ominous finding associated with mortality

rates of up to 60%.¹⁴ The lethality of hypothermia likely is not a consequence of the temperature itself but rather the relationship of hypothermia with underlying chronic diseases, shock, and an exaggerated inflammatory response. Although possible, the diagnosis should be questioned in patients lacking tachypnea or gas exchange abnormalities. Hypoxia is common in septic patients; more than 90% of patients will develop sufficient hypoxemia to require supplemental oxygen, generally correlating with a PaO₂/FiO₂ ratio less than 300. Tachycardia is a cardinal sign of sepsis, and unless patients have intrinsic cardiac disease or are taking nodal blocking medications, tachycardia is nearly universal. Abnormalities in circulating leukocyte count (more than 12,000 cells/mm³ or fewer than 4000 cells/mm³) are frequent enough to be considered important diagnostic criteria.

Several serum biomarkers are purported to have diagnostic and/or prognostic value, but none have demonstrated acceptable sensitivity and specificity for routine clinical use. The serum lactate level is suggested to be a marker of global hypoperfusion and tissue hypoxia in sepsis. According to the theory, even *before* patients develop frank hypotension, tissue perfusion is impaired by myocardial depression, relative hypovolemia from a leaky endothelium, increased metabolic demands, and impaired vasoregulatory mechanisms. Consequently, oxygen demand exceeds supply, and anaerobic production of lactate ensues. Not all agree that lactate production is a reliable marker of global hypoxia in sepsis.²⁹ One alternative explanation asserts that lactate production may be a regional, rather than global, phenomenon. Animal models of polymicrobial sepsis suggest that certain organs, particularly the liver and small intestine, may be more sensitive to impaired oxygen delivery.³⁰ Regardless of its exact mechanism of production, patients admitted with a sepsis-related diagnosis and elevated serum lactate levels (greater than 4 mmol/L) have an increased mortality rate.³¹ Further, septic patients with higher lactate clearance rates after 6 hours of therapy have decreased mortality rates.³² Procalcitonin and C-reactive protein, both markers of inflammation, have been studied as potential diagnostic tests for sepsis.^{33–35} The reported sensitivities and specificities of these tests vary widely, hence neither has achieved widespread acceptance. Measurements of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), a member of the immunoglobulin superfamily, remains experimental.³⁶ Interleukin (IL)-6, a cytokine mediator of inflammation, and D-dimer, a marker of coagulation, have substantial sensitivity but lack specificity for the diagnosis.^{37,38} Activated protein

C (APC) is an endogenous protein that attenuates microvascular thrombosis, and levels of this protein have been shown to be inversely correlated with outcomes.³⁹ IL-6, APC, and sTREM-1 assays are not readily available, so, despite decades of research, clinicians still yearn for a reliable test to diagnose sepsis.

Body fluid or tissue cultures are widely considered key to the sepsis diagnosis, but current evidence suggests that cultures may not be as pivotal as once thought. While cultures facilitate the diagnosis of infection, not all infected patients develop sepsis, and even fewer, severe sepsis.⁴⁰ Interestingly, a clear microbiologic explanation is absent in many patients.^{40,41} The likelihood of obtaining an initial positive blood culture increases with disease severity⁴² but remains surprisingly low. True positive blood culture rates are reported at about 8.1%,⁴³ and as many as half of all positive cultures are falsely positive, representing contamination.⁴⁴ Avoiding false-positive cultures is important because a positive culture prompts extra diagnostic tests, modifications of antimicrobial therapy, and adds significant costs even when the growth is eventually determined to be a result of contamination.⁴⁵ To confound matters further, “true-positive” cultures often do not reflect the sepsis-precipitating infection, as many positive cultures are obtained long after severe sepsis is established and represent insignificant colonization.

PATHOPHYSIOLOGY

Historically, sepsis was considered primarily—or perhaps solely—a disease of unbridled inflammation. One legacy of this view is the widely accepted consensus definition that highlights signs of inflammation as prerequisites to the diagnosis. This paradigm envisioned a multistage inflammatory cascade triggered by microbial invasion into a typically sterile body compartment or fluid. The subsequent proinflammatory state, while considered important to control the spread of local infection or injury, became dysregulated, and inflammation became destructive. In an effort to interrupt this sequence, numerous clinical trials tested the efficacy and safety of anti-inflammatory agents. These trials failed to consistently demonstrate a significant impact on mortality, even when quantitatively down-regulating serum mediators of inflammation (see **Box 1**). The lack of efficacy of anti-inflammatory compounds caused speculation that the pathophysiology of sepsis was more complicated than just uncontrolled inflammation, and discouraged research.

It is now clear that inflammation is just one of many contributors to septic physiology; other

Box 1**Controlled human studies of anti-inflammatory agents in sepsis**

High-dose corticosteroids
 Intravenous immunoglobulin
 Ibuprofen
 Prostaglandin E1
 Ketoconazole
 Platelet-activating factor receptor antagonist
 Platelet-activating factor-acetylhydrolase
 Murine anti-tumor necrosis factor (TNF) monoclonal antibodies
 Anti-TNF fab fragments
 TNF receptor fusion protein
 Interleukin-1 receptor antagonist

factors include enhanced coagulation and impaired fibrinolysis.^{1,46} The complex interplay between these pathways is fueled both by endogenous and exogenous factors. Exogenous sepsis triggers are typically protein, lipid, or carbohydrate microbial constituents. The most notorious exogenous microbial component is endotoxin, the integral cell wall component of gram-negative bacteria. Other well-recognized toxins are staphylococcal toxic shock syndrome toxin (TSST-1) and group B streptococcal toxin. Endogenous triggers—such as activated complement proteins, clotting cascade components, or dead host tissue—can also incite the pathophysiologic pathways of sepsis. Neither bacteremia nor endovascular infection is required for the development of sepsis; humoral release of toxic products from localized sites (such as an abscess) or the colon (as with gut translocation) can trigger a septic event.

Abnormal coagulation is nearly universal in severe sepsis.^{46,47} The hematologic dysfunction of sepsis is detectable by widely available laboratory assays. Although routine clotting tests (prothrombin and activated partial thromboplastin times) may be near normal, most patients will have elevated fibrin degradation products (fibrin split products and D-dimers) and depleted levels of specific clotting factors (namely, fibrinogen) and anticlotting proteins.⁴⁷

Early in the syndrome, tissue factor expressed by leukocytes and damaged endothelium, together with proinflammatory mediators, stimulate clotting factors V and VII, resulting in the production of thrombin. Initially, the accelerated thrombosis is attenuated by the host's natural anticlotting

proteins, namely protein C, protein S, and anti-thrombin. Over time, clot formation consumes clotting proteins, and anticlotting proteins are depleted as well. Sepsis also selectively impairs host conversion of inactive anticlotting precursors to active anticlotting proteins, and this impairment favors unabated thrombosis. As a second line of defense, fibrinolysis (primarily via plasminogen activation) is normally stimulated to dissolve the clots that threaten to clog the microvascular beds of critical organs. Unfortunately, the fibrinolytic system is also impaired by the production of thrombin, which increases levels of plasminogen activator inhibitor 1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI). Together, PAI-1 and TAFI combine to stabilize thrombi in microvascular beds, impairing tissue perfusion and contributing to organ failures.

ORGAN FAILURES***Pulmonary Failure***

Respiratory failure is common in septic patients with up to 75% requiring mechanical ventilation for an average of 7 to 10 days.¹⁹ Fortunately, fewer than 5% of patients will require chronic mechanical ventilation, and fewer than 10% will require oxygen 30 days after disease onset.⁴⁸ The mechanism of respiratory failure is complex and multifactorial. Work of breathing is increased in severe sepsis. Ventilatory demands are increased by hypoxia and compensation for the lactic acidosis of global hypoperfusion. Airflow resistance is increased and lung compliance is reduced.⁴⁹ These increased demands occur at a time when ventilatory power is compromised by diaphragmatic dysfunction and reduced respiratory muscle perfusion. This mismatch of supply and demand leads to combined hypoxic and hypercapnic respiratory failure.

Approximately half of all septic patients develop the most severe subset of acute lung injury (ALI), acute respiratory distress syndrome (ARDS). ALI results from a diffuse inflammatory injury to the lung and is characterized clinically by hypoxia and low pulmonary compliance. By consensus definition, ARDS is defined as a PaO₂/FiO₂ (P/F ratio) ratio less than or equal to 200 with bilateral infiltrates on chest radiograph in the absence of left atrial hypertension.⁵⁰ ARDS typically occurs early in the course of sepsis, with most afflicted patients manifesting characteristic signs and symptoms within 48 hours. Interestingly, there is only a rough correlation of P/F ratio with mortality until the ratio approaches 150, where the P/F ratio becomes a powerful predictor of death.⁵¹ Paradoxically, the chest radiograph adds little prognostic

information after the P/F ratio and lung compliance are considered.

Circulatory Failure

Hypotension sufficient to meet criteria for shock (systolic blood pressure [BP] less than 90, or a fall in systolic BP of more than 40 mm Hg, or mean arterial pressure less than 60 mmHg unresponsive to fluid administration) is present in about 50% of all septic patients at the time of diagnosis.⁵² Shock develops in approximately 50% of the remainder within the first few days of illness. As might be expected, of all organ failures, shock typically has the shortest duration, averaging only 1 to 2 days. "Chronic" shock is rare, as many patients die if prompt correction cannot be accomplished. Because pharmacologic elevation of blood pressure usually is achieved rather easily, mean arterial pressure of treated patients with "shock" does not differ from that of patients without shock, making mean arterial pressure a poor prognostic indicator. Clinicians can be lulled into a false sense of security if the quantity of vasopressor therapy administered is not taken into consideration. Data suggest that patients who require even low doses of a vasopressor after adequate volume replacement have a mortality rate approaching 40%, and the need for high doses of a vasoactive drug are associated with nearly a 60% mortality rate.¹⁸

Severe sepsis blunts myocardial contractility and mimics some aspects of cardiogenic shock. The myocardial depression of sepsis can cause elevated cardiac filling pressure and a low or low-normal cardiac output. One clue to distinguishing between the myocardial depression of sepsis and cardiogenic shock is the systemic vascular resistance (SVR). The SVR tends to be low in volume in resuscitated patients with septic shock and normal to high in pure cardiogenic shock, although there are exceptions to this rule. Also, the lack of focal wall motion abnormalities on echocardiogram may argue against cardiogenic shock, whereas global hypokinesis on echocardiogram might support the diagnosis of sepsis-related myocardial depression.

Renal Failure

Renal dysfunction commonly complicates sepsis. The Acute Kidney Injury Network (AKIN) defines acute kidney injury (AKI) as "an abrupt (within 48 hours) reduction in kidney function defined as an absolute increase in creatinine of either ≥ 0.3 mg/dL or a percentage increase of $>50\%$ (1.5-fold increase from baseline) or a reduction in urine output (oliguria of < 0.5 mL/kg/hour for > 6

hours)."²² In a medical ICU study, 56% of patients with severe sepsis met the AKI definition.⁵³ The AKIN definition predicts hospital mortality, need for renal replacement therapy (RRT), and length of stay. Fortunately, while oliguria and creatinine elevations are common, fewer than 15% of patients with sepsis progress to overt renal failure and receive RRT. Among those who require dialysis, the support is typically transient, as only 10% of critically ill patients with acute kidney injury will require chronic RRT.⁵⁴ Patients with premonitory renal impairment are most likely to experience this complication. Interventions that can minimize the incidence of AKI are prompt treatment of hypotension and avoidance of potentially nephrotoxic drugs, especially intravenous contrast and certain antimicrobials.

Metabolic Acidosis

Lactic acidosis is common in patients with severe sepsis but until recently, was considered a late indicator of hypoperfusion. It is now recognized that even in normotensive patients, significantly elevated serum lactate levels (>4 mmol/L) may occur and indicate a need for early and aggressive optimization of oxygen delivery. The pathogenesis of lactic acidosis is controversial and may be a result of low oxygen delivery (DO_2), maldistribution of cardiac output, or mitochondrial dysfunction. Boosting DO_2 to prevent or reverse anaerobic metabolism and lactic acidosis has been extensively studied. Evidence suggests that increasing DO_2 to an arbitrary supra-normal value in *established* sepsis may be ineffective, or even harmful.^{55,56} In contrast, *early* and vigorous resuscitation in the setting of elevated lactate or shock may be beneficial.⁵⁷

Coagulation Disorders

The incidence of coagulation disorders varies depending on the defining criteria, but most patients have reduced levels of clotting and anticlotting proteins and elevated clot degradation products.⁴⁶ Nearly 100% of sepsis patients have elevated D-dimer levels, and 90% have reduced protein C levels.⁵⁸ Likewise, modest thrombocytopenia (platelet counts, 75–100,000/mm³), minimal reductions in fibrinogen, and small prolongations of the prothrombin and partial thromboplastin times are common.^{47,58} Disseminated intravascular coagulation (DIC) occurs in about a third of severe sepsis cases, and it is a strong predictor of mortality, independent of APACHE II score and age.⁵⁹

Gastrointestinal Failure

Hepatic and bowel functions frequently are impaired in patients with severe sepsis. Gastric motility is reduced as splanchnic blood flow is shunted to other organs. Animal studies suggest that endotoxemia has a direct, but transient effect on gastric emptying.⁶⁰ Profound hypotension, especially when prolonged, also can lead to hepatocellular injury—so called “shock liver” characterized by mild increases in hepatic aminotransferases (AST and ALT) with a disproportionate increase in total bilirubin.⁶¹ Although controversial, hypoperfusion may impair the gut mucosa, facilitating bacterial translocation and reduced functional absorptive capacity.⁶² Gut ischemia is also largely responsible for the higher incidence of gastrointestinal (GI) bleeding seen in severe sepsis. In the distant past, significant upper GI bleeding occurred in nearly 30% of cases but the practices of early resuscitation and routine use of acid suppression have all but eliminated life-threatening GI bleeding.

Treatment

Sepsis treatment has evolved substantially to a few basic principles: prompt infection source control, culture of pertinent sites, early and appropriate empiric antibiotics, aggressive circulatory support, and noninjurious ventilatory support. For selected patients, recombinant human activated protein C (rhAPC) has been added to the treatment arsenal. Unfortunately, confidence in early studies reporting benefits of glycemic control and corticosteroids in shock has been eroded by subsequent publications. The Surviving Sepsis Campaign (SSC) guidelines, composed on behalf of numerous professional organizations, summarize and grade evidence for sepsis treatment.⁶³ Although not universally accepted, the guidelines are perhaps the most comprehensive summary of management practices. Several landmark trials provide evidence as to how effective recommended interventions can be when systematically applied.

Infection Control

Drainage of closed space infection, removal of infected foreign bodies, and debridement of devitalized tissue are believed to be important for source control in sepsis, even though no randomized trials support these practices. Because of the circumstantial evidence supporting the use of antimicrobials and strong belief they are effective, there are not, and likely never will be, randomized placebo-controlled trials of antibiotics, or even trials

intentionally delaying antimicrobial therapy. Typically, patients with sepsis have blood, urine, and sputum cultured; additional samples, such as wound drainage and ascitic, pleural, and cerebrospinal fluid cultures should be performed as indicated by the clinical scenario. The likelihood of making a culture diagnosis is maximized by obtaining specimens before antibiotics are initiated.

In the absence of definitive data regarding the importance of antimicrobial therapy, it is not surprising that a great deal of emotion is associated with the use of antibiotics. Despite their usefulness, antibiotics alone will never eliminate all severe sepsis. At best, antibiotics kill the offending pathogen; they do not reverse the inflammatory and coagulopathic cascades that likely have been active for hours to days. Nonetheless, the benefits of administering appropriate antibiotics appear to increase with escalating severity of illness and decrease with delays in administration. For instance, among noncritically ill patients with community-acquired pneumonia, faster treatment produces a very small survival benefit.⁶⁴ When patients are bacteremic⁶⁵ or sufficiently ill to be admitted to an ICU,⁶⁶ survival benefits appear larger. Obviously, because these studies are nonrandomized, their results must be interpreted cautiously since it is possible that potentially important covariates were not identified. For example, the reason for “inadequate” coverage is often that patients are infected with highly resistant or unusual organisms as the result of chronic illness, long hospital stays, previous antibiotic exposure, or an immunocompromised state. Despite study limitations, septic shock is probably a special situation where the time to deliver antimicrobial therapy has a powerful association with survival.⁶⁷ This report had two key findings: first, half or more of patients with septic shock did not receive antibiotics in the first 6 hours of illness and, second, with each passing hour of delay to antibiotic administration, observed mortality was higher.

Failure to respond to seemingly appropriate antimicrobial therapy may be the result of an undrained closed space infection (eg, empyema, intra-abdominal abscess), presence of a resistant organism(s), insufficient drug levels, or most commonly insufficient time for response after starting therapy. Many clinicians have an overly optimistic view of the speed with which antimicrobials improve physiologic and laboratory abnormalities. For example, among older patients with pneumonia, average time to resolution of fever is 7 days⁶⁸ and even in younger patients 4 or more days is often needed for resolution of fever.⁶⁹ Radiographic resolution of pneumonia in these studies typically requires weeks. Additional reports

indicate that 3 to 4 days may be needed for deferescence of hospitalized patients with what many physicians consider to be a minor problem, urinary tract infection.⁷⁰

Antibiotics should be chosen based on individual patient factors (eg, immunosuppression, allergies, and underlying chronic illnesses), the presumptive site of infection, pattern of local antibiotic resistance, and examination of body fluids/specimens. Unless the etiologic agent is known with a very high degree of certainty, broad-spectrum antibiotic coverage is indicated until culture and sensitivity data are known. The rationale for use of broad-spectrum therapy comes from the observed association of worse outcomes with inappropriate initial antimicrobial therapy.^{65,66} Unfortunately, changes in resistance patterns induced by indiscriminate past antibiotic use now frequently necessitate three or sometimes even four antibiotics for empiric coverage. The stark reality is that it is not possible to anticipate or provide empiric therapy for all possible organisms. Within reason, it is best to begin therapy in the critically ill patients with “too broad” a spectrum and then narrow coverage as more clinical data become available. With that caveat, antibiotic coverage should be reassessed on a daily basis and unnecessary drugs should be stopped promptly. Contrary to popular belief, antibiotic therapy is not benign. Use of excessive or unnecessary antibiotics is costly, risks allergic reactions and drug toxicity, and perhaps most importantly, breeds the emergence of highly resistant bacteria that can harm future patients.

Respiratory Support

Most patients with severe sepsis develop some degree of acute lung injury (ALI). In a landmark study of patients largely with sepsis-related ALI, investigators established that use of a 6-mL/kg tidal volume indexed to predicted body weight (PBW) reduced absolute mortality by 9% compared with ventilation with a traditional tidal volume of 12 mL/kg.⁷¹ This practice is commonly known as “low tidal volume” mechanical ventilation; however, the 6-mL/kg tidal volume strategy is actually a *normal* tidal volume; it just happens to be lower than the volumes used traditionally. In the lower volume arm of the study, the tidal volume was adjusted from that used before enrollment to 6 mL/kg PBW but could be reduced as low as 4 mL/kg if needed to maintain plateau pressures below 30 cm water. Data from clinical practice now suggest use of higher tidal volumes in ALI is associated with worse outcomes. Further, patients *without* ALI who are ventilated with higher

tidal volumes, are more likely to develop lung injury.⁷² Given that a normal tidal volume strategy does not add cost, or require additional sedation or paralysis, and is simple to implement, it represents a reasonable starting point for ventilation of ALI patients.

Positive end expiratory pressure (PEEP) inhibits atelectasis and attenuates development of ALI in animal models of lung injury, and some nominal level of PEEP (~5 cm H₂O) should probably be supplied to all patients with sepsis-related ALI. Beyond this minimal recommendation, the selection of PEEP and inspired oxygen concentration should maintain saturations in the 88% to 95% range (or equivalent PaO₂'s) while avoiding potentially toxic inspired oxygen concentrations and excessive lung stretch. In a large randomized controlled trial of ALI patients ventilated with 6-mL/kg tidal volume, there was no difference in clinical outcomes between a lower-PEEP versus a higher-PEEP strategy.⁴⁸ Those results have now been validated by two additional trials.^{73,74} So, in patients with lower tidal volumes, neither higher levels of PEEP nor titration of PEEP to lung compliance have been shown to produce consistently superior outcomes. Ventilation strategies that give a high priority to “recruitment” clearly can improve radiographic images of the lung, and indices of oxygenation, but to date do not translate into improved patient outcomes.^{75,76}

Cardiovascular Support

In the setting of severe sepsis, circulatory failure is defined typically as a systolic blood pressure (BP) less than 90 mm Hg, a decrease in normal systolic BP of more than 40 mm Hg unresponsive to fluid challenge (20–30 mL/kg), or a mean arterial pressure below 60 mm Hg. At the onset of the syndrome, most patients with sepsis-induced shock have substantial volume depletion with variable degrees of systemic vascular dilation and myocardial dysfunction. Ventricular filling pressures are usually low because patients have been deprived of oral intake, have increased fluid losses (from sweating, panting, vomiting, or diarrhea), have dilated capacitance vessels, and increased endothelial permeability. The average septic patient needs 4 to 6 L of crystalloid replacement, or a comparable volume-expanding amount of colloid, within the first few hours to optimize ventricular performance.⁵⁷ Wide disparities in practice are observed in the fluid volume infused, the rate of administration, or method of monitoring resuscitation adequacy. It seems each physician has a different level of comfort with regard to the amount of fluid infused before instituting invasive monitoring

or starting a vasoactive drug. Regardless, when a fluid challenge is used, it is important to use a bolus of sufficient volume to cause a detectable change. A commonly selected "bolus" size, 500 mL, has been shown to make no measurable change in blood pressure, intravascular filling pressures, or cardiac output.⁷⁷ Thus, it makes sense use larger fluid challenges (~15 mL/kg of crystalloid). Likewise, it is logical to administer the bolus as rapidly as possible to maximize the hemodynamic effect.

In general, there is no certain difference in efficacy of crystalloid or colloid in the initial resuscitation of septic patients. However, a recent study comparing 10% pentastarch, a low-molecular-weight hydroxyethyl starch (HES 200/0.5), with modified Ringer's lactate demonstrated that pentastarch administration was associated with higher rates of acute renal failure and RRT.⁷⁸ One systematic review suggests that crystalloids may be more efficacious in general for resuscitation,⁷⁹ whereas a large randomized controlled trial of ICU patients comparing resuscitation with normal saline versus 4% albumin showed no significant differences in pertinent clinical outcomes.⁸⁰ A smaller volume of colloid will be required to achieve any given increase in intravascular pressure; however, neither colloid nor crystalloid is confined entirely to the vascular compartment. Although less colloid is required, volume expansion is achieved at substantial cost. Colloid risks allergic reactions and may be priced 20 to 100 times that of an equivalent dose of crystalloid. Because hemodilution accompanies resuscitation with colloid or crystalloid, administration of packed red blood cells is sometimes required to maintain hemoglobin concentrations in an acceptable range.

For patients who are hypotensive after a fluid challenge or who have lactate elevations, use of an explicit hemodynamic protocol can reduce hospital mortality by as much as 16%.⁵⁷ This early goal-directed therapy (EGDT) differs in numerous respects from older unsuccessful studies in which attempts were made to boost oxygen delivery later in the course of sepsis.⁸¹ Although the difference in outcomes might simply be the timing of the intervention, it is likely that some or all protocol elements are essential. This strategy uses vasopressors to achieve a mean arterial pressure greater than 65 mm Hg after central venous pressure (CVP) is raised to 8 to 12 mm Hg with fluids. A key distinction between this and other approaches is the measurement of superior vena caval oxygen saturation (ScVO₂), targeting a value greater than 70%. This goal is achieved by red blood cell transfusion for anemic patients (hematocrit < 30%) and dobutamine for patients above that threshold.

Application of these rules for a mere 6 hours reduced mortality, the fraction of patients requiring mechanical ventilation and vasopressors, hospital length of stay, and hospital costs.⁵⁷

Like many severe sepsis therapies, controversy and questions surround this treatment. Some question how protocolized administration of packed red blood cells reconciles with earlier data suggesting a lower transfusion target may be acceptable or even beneficial.⁸² One plausible explanation would be that septic shock patients are hemodynamically unstable, thus they differ significantly from the stable participants studied in previous transfusion protocols.⁸³ It is also important to recognize that transfusion was but one part of a complex protocol, and the consequences of applying that protocol without transfusion are unknown. While some practitioners have raised concerns about the risk of transfusion-associated lung injury (TRALI) in this setting, it appears that even if TRALI risk is increased, the net effect of the whole protocol is positive. Another important unanswered question is what is the maximum time window for application of this protocol beyond which benefit wanes? This question is especially important given that studies in which later attempts to modify oxygen delivery may have been harmful. Despite impressive results, this protocol has not been widely adopted,⁸⁴ possibly because of the relatively small number of patients studied, or the single-center and nonblinded study design. Other potential reasons for nonimplementation are inadequately staffed emergency departments, the lack of equipment needed to measure central venous pressure or venous saturation, and controversy regarding protocol efficacy.⁸⁵

After resolution of shock, data from the NHLBI Fluid and Catheter Treatment Trial (FACTT) indicate that among patients with ALI, a more conservative approach to fluid management is prudent.⁸⁶ Although not exclusively a study of severe sepsis, nearly two thirds of participants met criteria for severe sepsis (pneumonia or sepsis as the ALI risk factor). Application of an explicit hemodynamic management protocol that targets a CVP (< 4 mm Hg) or pulmonary capillary occlusion pressure (< 8 mm Hg) after resolution of shock resulted in a significantly less positive net fluid balance during the first week of treatment. Although the nominally lower mortality (~3%) was not significantly different, fluid conservative patients had more ventilator- and ICU-free days and a reduced duration of mechanical ventilation among survivors. These goals were reached without increased risk of renal insufficiency or hypotension. The tool used to measure the vascular pressure (CVC versus PAC) did not seem to matter, except with regard to

complications where PAC-randomized patients had roughly twice as many nonfatal catheter-related complications.⁸⁷

While vasopressors are a mainstay of septic shock management, surprisingly little data are available to guide their use. Small randomized studies suggest norepinephrine is more likely to rapidly achieve a desired blood pressure target than other vasopressors, and do so with less tachycardia.⁸⁸ One large cohort observational study, the Sepsis Occurrence in Acutely ill Patients (SOAP) study, suggests that use of dopamine in uncontrolled practice is associated with a higher mortality than use of norepinephrine.⁸⁹ Although several studies now suggest that dopamine does not offer significant protection of the kidney at risk from shock or sepsis, it is still ordered by some physicians for that purpose.⁹⁰ The past few years have produced numerous reports that some septic shock patients have low vasopressin levels and that fixed dose replacement can reduce or eliminate the need for catecholamines.⁹¹⁻⁹³ The Vasopressin and Septic Shock Trial (VASST) compared low-dose vasopressin and norepinephrine versus norepinephrine alone, and demonstrated no differences in 28-day or 90-day mortality.⁹⁴ However, in an analysis of subgroups defined a priori, a trend toward mortality benefit was observed in patients with lower norepinephrine requirements who were treated with vasopressin.⁹⁴ These data are hypothesis generating and suggest more study is needed to clarify the role of vasopressin.

Steroids

Numerous trials using short courses of high-dose corticosteroids in patients with severe sepsis have failed to demonstrate improved survival.⁹⁵ In one frequently cited study using lower steroid doses, 300 patients enrolled within 8 hours of shock onset were randomized to receive hydrocortisone plus fludrocortisone or placebo for 7 days.⁹⁶ When evaluating all patients, time to death may have been altered somewhat, but there was no significant difference in primary study end points of 28-day, ICU, hospital, or 1-year mortality between treated and placebo recipients. Evaluation of secondary end points found that for patients who failed to increase their total plasma cortisol levels by at least 9 µg/dL after 250 µg ACTH stimulation (so-called "nonresponders"), there was approximately a 10% absolute reduction in adjusted mortality associated with treatment. The "responders" to ACTH stimulation had a nominally higher mortality if treated compared with placebo, although this difference was not statistically significant.⁹⁶ This study caused

controversy and stimulated additional study. Since benefit appeared to be confined to ACTH nonresponders, perhaps the most pressing unanswered question is whether an ACTH stimulation test is necessary. This is a significant issue in many hospitals where cortisol results are not available for days. Subsequent studies report a poor correlation between free and total cortisol levels, raising doubt as to the soundness of using total cortisol values.⁹⁷ Another problem is clinician skepticism that patients with high baseline cortisol values could benefit from even more glucocorticoid merely because they failed to raise plasma cortisol after ACTH. Along those lines, some researchers claim a more relevant provocation may be 1 µg of ACTH.^{98,99} Some physicians have also expressed doubt regarding the need to include fludrocortisone because of the volume of fluids that have been administered and the mineralocorticoid effects of hydrocortisone.¹⁰⁰

Further evidence questioning the effectiveness of corticosteroids in sepsis came from post hoc analysis of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial. In this analysis, patients given steroids in a nonrandomized manner as part of usual practice still demonstrated a survival benefit with drotrecogin alpha (activated).¹⁰¹ Despite these questions, a number of clinicians have adopted glucocorticoid therapy for severe sepsis patients without shock, or with shock of prolonged duration, perhaps based on the recommendations of some authors for broad use.¹⁰²

The Corticosteroid Therapy of Septic Shock (CORTICUS) study was a large, randomized controlled trial comparing hydrocortisone versus placebo in patients with septic shock done in an effort to help clarify the role of corticosteroids.¹⁰⁰ Results of the trial suggest little benefit of corticosteroids in patients with septic shock. In both the "ACTH responders" and the "ACTH nonresponders," there was no significant difference in the primary outcome, 28-day all-cause mortality. Of note, patients in the hydrocortisone group did have faster resolution of shock, but there were more episodes of superinfection, including new sepsis and septic shock.¹⁰⁰ On balance, corticosteroids have a limited use in the management of shock and should probably be limited to those with refractory shock and a history of chronic steroid use and patients proven to have absolute adrenal insufficiency.

Human Recombinant Activated Protein C

Drotrecogin alfa activated, also known as human recombinant activated protein C (rhAPC), is the

only sepsis-specific medication proven to have a mortality benefit.¹⁹ rhAPC reduces inflammation, down-regulates coagulation, and inhibits the antithrombotic actions of PAI-1 and TAFI. The PROWESS trial, a large randomized controlled trial comparing rhAPC to placebo in patients with severe sepsis, demonstrated an absolute mortality reduction of approximately 6% in the treatment group.¹⁹ Long-term follow-up demonstrated a persistent survival benefit 2 to 3 years after treatment.¹⁰³ In addition, treated patients had a shorter time on vasopressors and mechanical ventilation compared with placebo.¹⁰⁴

The treatment effect appears to be time sensitive. A large open-label trial and a multihospital case series found that patients treated with rhAPC within the first day after developing severe sepsis had a higher survival rate as compared with the second day. Earlier treatment was also associated with a shorter time on ventilator, in the ICU, and in the hospital.¹⁰⁵ A large retrospective analysis of all patients treated in controlled trials in the first 24 hours of sepsis compared with those in the second 24 hours of sepsis supports the observation that earlier is better than later treatment.¹⁰⁶

The sole toxicity of rhAPC is bleeding, seen in 1.5% to 2.5% more patients than those not treated (a risk comparable in magnitude to anticoagulation with heparin). The risk of serious bleeding can be minimized by avoiding administration to patients with fewer than 30,000 platelets/mm³, overt hemorrhage, recent stroke, or intracranial or spinal surgery. Avoiding treatment within 12 hours of surgery or trauma, and stopping the drug for 2 hours before performing invasive vascular procedures also minimizes bleeding risk.

In a post hoc subgroup analysis of the PROWESS population, patients with a modified APACHE II score of 25 or higher (ie, those with a "high risk" of death), had an absolute mortality reduction of 13%.¹⁰⁷ As with any subgroup analysis, designating one population with a larger survival benefit than the whole dictates that there must be a complementary group with a lesser benefit. Subsequent study of a heterogeneous group of "low risk" of death patients confirmed that such patients do not experience a survival benefit yet still incur the roughly 1% to 2% increase in serious bleeding risk compared with placebo.¹⁰⁸ Therefore, rhAPC is approved for the treatment of severe sepsis in adult patients at high risk of death.

A major impediment to widespread use of rhAPC has been its substantial cost, approximately \$7000 per course of therapy. For many clinicians, the survival benefit, and data suggesting a shorter time on mechanical ventilation, in shock,

in the ICU, and in the hospital compared with placebo is not sufficiently compelling to justify the financial costs of rhAPC, despite numerous analyses suggesting cost-effectiveness.^{7,109,110}

Glucose Control

Hyperglycemia impairs immune functions¹¹¹ and may exert a procoagulant effect, but the role of glucose control in the management of critically ill patients is still evolving. A pivotal study of surgical patients demonstrated that stringent control of glucose (80–110 mg/dL) reduced the risk of death and severe sepsis when compared with more liberal glucose management.¹¹² Studies to confirm these observations in medical patients have failed to reproduce such results. A follow-up single-center, unblinded trial compared tight glucose control (80–110 mg/dL) to conventional glucose control in 1200 medical ICU patients. In the intention-to-treat population, there was no difference in 28-day mortality between the two groups; however, patients in the intensive insulin therapy arm had less acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital.¹¹³ Unfortunately, but perhaps not surprisingly, more hypoglycemia was observed in the tight glucose control group. Analogous to the rhAPC trials, a subgroup analysis identified a group of patients (those requiring >3 days in the ICU) who had a mortality benefit and a complementary group (patients requiring <3 days in the ICU) with a greater mortality in the intervention group. This subgroup analysis is useful for further hypothesis generation.

The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study was a two-by-two factorial trial examining both tight glycemic control and volume substitution strategies in sepsis.⁷⁸ With respect to glycemic control, this multicenter trial of septic patients in multidisciplinary intensive care units compared tight glucose control (80–110 mg/dL) with conventional glucose control (180–200 mg/dL). The trial was terminated prematurely secondary to safety concerns. One concern was that the rate of severe hypoglycemia, defined as a glucose level less than 40 mg/dL, was higher in the intensive therapy group than in the conventional therapy group (17.0% versus 4.1%, $P < .001$). Despite effectively lowering serum glucose levels, patients in the intensive glucose control arm had no differences in 28-day mortality or mean score for organ failures.

As these and other studies demonstrate, tight glycemic control is not a trivial undertaking and is associated with risk of hypoglycemia. Strict glycemic control usually requires a continuous insulin

infusion with hourly monitoring of blood glucose, and this practice is nursing-intensive. Given the risks of hypoglycemia, lack of demonstrable mortality benefit, and mixed evidence regarding organ failures, the future of tight glycemic control as a pillar of sepsis management in medical patients remains unclear. Further study is needed to define the best population and the best protocol for such therapy.

Therapy of Metabolic Acidosis

Lactic acidosis is common in severe sepsis patients. Fortunately, it is usually a mild and self-limited problem that resolves when intravascular volume deficits are corrected. When lactic acidosis results from low cardiac output and hypotension, it is likely to be improved by increasing arterial pressure. Conversely, when cardiac output and arterial pressure are normal or high, no data convincingly demonstrate a benefit of further increasing output. Survival correlates best with lactate levels and not serum pH. Therefore, buffering an abnormal pH with sodium bicarbonate¹¹⁴ or dichloroacetate¹¹⁵ does not improve outcome, unless the underlying reason for lactate generation is corrected simultaneously. Even though experimental data do not support the practice, as a practical matter, many physicians feel compelled to intervene when pH declines below 7.10.

SUPPORT OF THE KIDNEY

The kidneys commonly experience transient dysfunction early in the septic process; more than 40% of patients develop transient oliguria, which is usually reversed by simple fluid administration to correct underlying hypovolemia. For patients with shock, a combination of volume repletion and vasoactive drug administration may be required to raise cardiac output or SVR sufficiently to perfuse the kidneys. Diuretic therapy has not been shown to improve outcome in critically ill patients with acute renal failure.¹¹⁶ Avoidance of nephrotoxic agents, such as intravenous contrast is prudent, and clinicians should be aware that many antimicrobial agents can adversely affect renal function.

A fraction of patients with sepsis-induced acute kidney injury will require RRT. Intermittent high-flow hemodialysis has been the traditional method for renal replacement in critically ill patients, particularly in the absence of shock. Continuous hemofiltration is growing in popularity. Because it avoids rapid fluid shifts and can be performed by ICU nurses, it has become the preferred method of many nephrologists and intensivists, especially

for patients with shock. Despite decades of experience with RRT in critically ill patients, the optimal intensity of RRT—ie, the number of days per week to apply intermittent hemodialysis, or the flow rate to target in continuous hemofiltration—has been controversial. A recent study randomized 1124 critically ill patients to either a more intense, or less intense RRT regimen.¹¹⁷ The more intense RRT arm had intermittent hemodialysis dosed 6 days per week or continuous hemofiltration rates of 35 mL/kg/h, whereas the less intense RRT arm had intermittent dialysis 3 days per week or continuous hemofiltration rates of 20 mL/kg/h. There was no significant difference between the two groups in the duration of RRT, rate of kidney function recovery, or rate or nonrenal organ failures, and intensive RRT did *not* decrease mortality.¹¹⁷

Nutritional Support

As with other critically ill patients, there are two basic “truths” about nutrition. First, prolonged starvation (weeks to months) is fatal, and second, any patient can tolerate a few days without feeding. Almost every other aspect of nutritional support is argued. Even with the disagreements about nutrition, there are some common practices. Nutritional support usually is withheld at least until hemodynamic stability is achieved (1 to 2 days).^{118,119} Most practitioners now favor the enteral route of support because it provides more complete nutrition, preserves gut mucosa, and favorably impacts immune function. In addition, enteral nutrition is substantially less expensive than intravenous supplementation and avoids the complications associated with the central venous catheters and hypertonic glucose solutions required for effective parenteral nutrition.

At this time, there is no compelling evidence to suggest that any particular enteral feeding formula or particular balance of components is superior to another for the patient with severe sepsis, but there are compelling phase II data from patients with acute lung injury. Three trials now suggest that an enteral formula enriched with omega-3 fatty acids, antioxidants, and other specialized ingredients may improve outcomes.^{120–122} Pending results of a definitive study of specialized tube feeding now under way, current knowledge supports giving a balanced mixture of carbohydrate, protein, and lipid based on the patient’s estimated needs. For patients with prolonged (>7 days) gut dysfunction, parenteral nutrition may be indicated.

SUMMARY

Severe sepsis is a common syndrome but because it has variable presentations in patients of

all ages and with a wide range of underlying diseases it can be difficult to identify. This problem is compounded by absence of a reliable diagnostic test. Even though there is scientific debate regarding several severe sepsis treatments, an organized approach applied by trained physicians and nurses in which all applicable treatments are applied as rapidly as possible has consistently been shown to reduce mortality and morbidity.

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