Severe Sepsis and Septic Shock: Epidemiology, Pathophysiology, Diagnosis, and Management

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Severe sepsis is the 10th leading cause of death in the United States and the most common cause of death among critically ill patients in noncoronary ICUs. In 2001, approximately 750,000 cases of severe sepsis occurred, and the incidence continues to increase. The US Centers for Disease Control and Prevention estimates the annual cost of hospital care for sepsis to be approximately $6 billion per year in the United States. As such, severe sepsis is an important public health problem.

DEFINITIONS

In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference proposed a broad framework to define the systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis (Table 1 on page 168). It was envisioned as a continuum of worsening inflammation, starting with SIRS and evolving from sepsis to severe sepsis and ultimately septic shock. The criteria for SIRS are based on temperature, heart rate, respiratory rate, and white blood cell count. At least 2 of these 4 criteria must be met to define SIRS. Although SIRS often occurs in the
Table 1.
Criteria for Sepsis, Severe Sepsis, and Septic Shock Based on the 1991 ACCP/SCCM Consensus Conference

<table>
<thead>
<tr>
<th>Term</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>SIRS</td>
<td>2 of the 4 following criteria:</td>
</tr>
<tr>
<td></td>
<td>Temperature &gt;38°C (100.3°F) or &lt;36°C (96.7°F)</td>
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<tr>
<td></td>
<td>Heart rate &gt;90/min</td>
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<tr>
<td></td>
<td>Hyperventilation evidenced by respiratory rate &gt;20/min or arterial CO₂ &lt;32 mm Hg</td>
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<tr>
<td></td>
<td>White blood cell count &gt;12,000 cells/µL or &lt;4,000 cells/µL</td>
</tr>
<tr>
<td>Sepsis</td>
<td>SIRS criteria with presumed or proven infection</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>Sepsis with organ dysfunction</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Sepsis with hypotension despite adequate fluid resuscitation</td>
</tr>
</tbody>
</table>

ACCP, American College of Chest Physicians; SCCM, Society of Critical Care Medicine; SIRS, systemic inflammatory response syndrome.

Setting of infection, noninfectious conditions, such as burns, acute pancreatitis, and trauma, can lead to SIRS. Sepsis is defined as the presence of SIRS and a source of infection. Severe sepsis is defined as sepsis accompanied by organ dysfunction.

Although the 1991 Consensus Conference laid the framework to define sepsis, it had important limitations. The “2 out of 4” criteria for SIRS and the thresholds were somewhat arbitrary and not specific to sepsis alone. The criteria did not include biochemical markers such as C-reactive protein, procalcitonin, or interleukin (IL)-6, all of which are elevated in sepsis. The 2001 Consensus Conference of the Society of Critical Care Medicine, European Society of Intensive Care Medicine, American College of Chest Physicians, American Thoracic Society, and Surgical Infection Society modified these definitions. The criteria for sepsis were revised to include infection and the presence of any of the diagnostic criteria shown in Table 2 on page 168. These criteria were based on an expansion of the clinical and laboratory parameters. The conference participants acknowledged that there was no single parameter or set of clinical or laboratory parameters that are adequately sensitive or specific to diagnose sepsis. The severe sepsis criteria remained unchanged. Although there are several criteria to define organ dysfunction during sepsis, the use of the Sequential Organ Failure Assessment score by Vincent and colleagues was recommended to define organ dysfunction during sepsis. A more explicit definition for septic shock was also

Table 2.
Criteria for Sepsis Based on the 2001 SCCM/ACCP/ATS/ESCIM/SIS Consensus Conference

<table>
<thead>
<tr>
<th>Term</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Infection with any 1 of the following clinical or laboratory criteria:</td>
</tr>
<tr>
<td>Clinical criteria</td>
<td>Fever, hypothermia, tachycardia, altered mental status, arterial hypotension, decreased</td>
</tr>
<tr>
<td>Laboratory criteria</td>
<td>urine output, significant peripheral edema, positive fluid balance</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis, leukopenia, hyperbilirubinemia, hyperglycemia, increased C-reactive protein, procalcitonin or creatinine, coagulation abnormalities, increased cardiac output, reduced mixed venous oxygen saturation</td>
</tr>
</tbody>
</table>

ACCP, American College of Chest Physicians; ATS, American Thoracic Society; ESCIM, European Society of Intensive Care Medicine; SCCM, Society of Critical Care Medicine; SIS, Surgical Infection Society.
proposed: hypotension with a systolic blood pressure less than 90 mm Hg or a mean arterial blood pressure (MAP) less than 70 mm Hg, despite adequate fluid resuscitation.

Despite these attempts to define sepsis, severe sepsis, and septic shock, early recognition remains a challenge. Tissue hypoperfusion can occur in the absence of hypotension and could be present for hours before organ dysfunction manifests.

**Epidemiological Characteristics**

**Incidence and Mortality**

In the United States, the incidence of severe sepsis is estimated to be 300 cases per 100,000 population. Approximately half of these cases occur outside of the ICU. A fourth of patients who develop severe sepsis die during their hospital stay. Septic shock is associated with the highest mortality, approaching 50%. The cumulative burden of organ failure is the strongest predictor of death, in terms of both the number of organs failing and the degree of organ dysfunction.

In 2003, Martin and colleagues found an increase in sepsis incidence and sepsis-related deaths over the past 2 decades in the United States. This trend is expected to continue given the aging population, increasing burden of chronic health conditions, and increased use of immunosuppressive therapy, transplantation, chemotherapy, and invasive procedures. National estimates of the incidence of severe sepsis are based on the use of administrative data sets. Changes in coding practices, particularly the increased coding of organ dysfunction, may overestimate the rate of increase.

Although the total mortality attributed to sepsis has increased over the past 2 decades, the case-fatality has declined. This may be due to nonspecific advances in medical care for the critically ill. Length of stay has also declined as patients are increasingly discharged to long-term acute care facilities during recovery, which leads to underestimation of the case-fatality rate.

**Cause and Site of Infection**

Although gram-negative infections accounted for the majority of cases a decade ago, gram-positive infections are currently the most common cause of sepsis. Critically ill patients are increasingly stricken with resistant strains of bacteria, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, quinolone-resistant *Pseudomonas aeruginosa*, and fungi, especially the *Candida* species.

Respiratory tract infections, particularly pneumonia, are the most common site of infection. Other types of infection include genitourinary, abdominal, skin, and soft tissue infections; device-related infection; central nervous system infection; and endocarditis.

**Risk Factors**

Increased age, male gender, African American race, and chronic health conditions are important risk factors for severe sepsis. The incidence of severe sepsis increases disproportionately in older adults, and more than half of severe sepsis cases occur in those older than 65 years. More than half of the patients who develop severe sepsis also have at least one chronic health condition. Severe sepsis is more likely to occur in individuals with chronic obstructive pulmonary disease, cancer, chronic renal and liver disease, and diabetes mellitus. Other risk factors include residence in a long-term care facility, malnutrition, and the use of immunosuppressive medications and prosthetic devices. Finally, abnormalities in the immune response to infection, as described later, increase the risk of infection and severe sepsis. These abnormalities can be secondary to chronic diseases or age (immunosenescence).

Risk factors that increase susceptibility to severe sepsis also increase mortality following severe sepsis. For instance, increased age, male gender, and chronic health conditions increase mortality after severe sepsis. The most important in-hospital risk factors are the severity of illness and the number of organs failing.

Despite improved understanding of clinical risk factors influencing susceptibility to and outcomes of sepsis, it
remains unclear why some subjects develop severe sepsis and succumb to the infection whereas others do not. Thus, genetic factors have been examined to explain variability in susceptibility and outcomes of infection. A study by Sorensen and colleagues suggests that genetic factors may be more important to the outcomes of infectious diseases compared with cardiovascular disease. In this study, children whose parents died from infectious causes had 5.8-fold increased risk of dying because of infections. In comparison, the increased risk of death due to cardiovascular causes was 4.5-fold if the children’s parents died of cardiovascular causes. Because sepsis is common and often fatal, the pattern of inheritance is unlikely to be Mendelian, where phenotypical differences are attributed to a single gene. Multiple genes may interact with pathogens (environmental factors) and influence susceptibility and outcome of sepsis. Some of these candidate genes have shown promising results in preliminary studies include tumor necrosis factor (TNF), plasminogen activator inhibitor-1, Toll-like receptor (TLR)-1 and TLR-4, and the MAF functional variant required for downstream signaling of TLR-2 and TLR-4. The relative contribution of clinical and genetic factors to the susceptibility and outcomes of severe sepsis is not defined. Genetic factors may play an important role in younger individuals but could be less important in older adults, for whom chronic diseases may play a more important role. Furthermore, common variants may carry a smaller attributable risk whereas certain rare variants may lead to a higher attributable risk. Recent advances in technology using genome-wide scans, whereby more than 1 million polymorphisms can be assayed in a single individual, may allow the identification of novel genetic variants.

PATHOPHYSIOLOGICAL CHARACTERISTICS

The innate immune system plays a vital role in resistance to infectious disease. Components of the innate immune response form the first line of defense in the recognition and destruction of pathogens and allow time for the acquired immune response to be effective. The innate immune system consists of physical and chemical barriers and humoral and cellular mediators. Components of the innate immune response form the first line of defense in the recognition and destruction of pathogens and are characterized by their rapid action, their lack of immunological memory, and their function as antigen-presenting cells that activate the adaptive immune system. The principal cellular components of the innate immune system include neutrophils, monocytes and macrophages, natural killer cells, and dendritic cells. These cells are able to recognize pathogens through the use of TLRs, described subsequently. The host–microbe interaction leads to the activation of several mediators within the innate immune system, including proinflammatory and anti-inflammatory cytokines and the coagulation cascade. The pathophysiological process of sepsis is complex and involves the interaction of different pathways. Key mechanisms are described briefly next.

Host–Microbe Interaction

Pathogen-associated molecular patterns (PAMPs), such as endotoxins or lipopolysaccharides (LPS) in gram-negative bacteria, are highly conserved molecular structures within bacterial cell walls. These molecular patterns are recognized by cells of the innate immune system. Lipopolysaccharide on gram-negative bacterial cell wall plays an important role in recognition. Although there is no LPS equivalent for gram-positive bacteria, components of the bacterial cell wall, such as lipoteichoic acid or peptidoglycan and exotoxin, could play a similar role.

In 1997, Medzhitov and colleagues described the TLRs in Drosophila. This discovery was followed by the identification of TLRs in mice and humans. These receptors play a critical role in recognizing PAMPs and instructing the adaptive immune system to respond to infection. For instance, LPS binds to LPS-binding protein (LBP), a circulating mediator, and to cluster of differentiation (CD)14, located on the membrane of immune cells. This complex of LPS–LBP and CD14 signals through TLR-4 and eventually leads to nuclear translocation of nuclear factor-κB and activation of cytokines.
More than 10 TLRs have been discovered with unique ligands, such as TLR-4, which is an LPS receptor; TLR-2, which recognizes gram-positive cell walls; and TLR-5, which is a receptor for flagellin. Although it was initially perceived that each TLR may interact with only a single microbial ligand, recent work suggests that different ligands can activate a single TLR. The role of TLR-4 in sepsis is an area of intense study, and two TLR-4 antagonists are currently in phase 3 clinical trials for the treatment of severe sepsis.

A further layer of complexity has been introduced by the discovery of additional pathways to mediate the recognition of PAMPs. These include cell surface molecules, such as macrophage scavenger receptor, CD11b/CD18 receptors, and nucleotide-binding oligomerization domain-1 and -2 proteins, located intracellularly.

The end result of these complex steps is the activation of the humoral and cellular mediators. Humoral mediators that are expressed include key proinflammatory proteins, such as TNF, IL-6, and inducible nitric oxide synthase, and an almost simultaneous expression of antiinflammatory proteins, such as IL-1 receptor antagonist and IL-10.

The activation of humoral and cellular mediators is necessary for an adequate, controlled host response. Understanding how and why this initial response leads to the unwanted downstream sequelae that characterize sepsis and the multiple organ dysfunction syndrome (MODS) has been more difficult. Some of the potential mechanisms that underlie severe sepsis susceptibility are discussed subsequently.

**Uncontrolled Inflammation**

In 1972, Lewis Thomas proposed that sepsis is a condition of overly exuberant and uncontrolled inflammation. Although activation of the innate immune response is necessary to eradicate infection, it can be overwhelming and can lead to severe sepsis and death. The terms *uncontrolled, maladaptive, and dysregulated* are often used to describe inflammation in sepsis. This theory was based on animal models of sepsis in which high circulating concentrations of proinflammatory mediators, such as TNF, IL-1, and IL-6, were observed. However, several randomized clinical trials in humans antagonizing proinflammatory cytokines and anti-endotoxin strategies have failed to improve survival or have worsened it. These results have challenged the theory of uncontrolled inflammation.

Several reasons have been suggested to explain failure of immunomodulatory strategies. First, severe sepsis is a heterogeneous disorder. Immunomodulatory therapy could be appropriate for patients with an uncontrolled response to infection but detrimental in patients with an appropriate, controlled response. Second, the timing of therapy may play a role. Most patients who present to the hospital for treatment of infection and sepsis already have increased circulating concentrations of cytokines and therefore may be less likely to benefit from cytokine modulation. Two cytokines are thought to be late mediators of sepsis, macrophage inhibitory factor and high-mobility group box-1, and therapies targeted at these cytokines have shown encouraging results in animal studies. For example, therapies targeting macrophage inhibitory factor and high-mobility group box-1 that were initiated up to 96 hours after initiation of sepsis showed beneficial effects.

**Coagulation Cascade**

The positive phase 3 trial of recombinant activated protein-C (drotrecogin alfa) in patients with severe sepsis renewed interest in understanding the effects of the coagulation pathway in severe sepsis. During sepsis, coagulation proteins are activated, and anticoagulation (protein C system and tissue factor pathway inhibitor) and fibrinolysis (plasminogen activator inhibitor-1) pathways are impaired. Inflammatory mediators, such as TNF, initiate coagulation through the induction of tissue factor expression, primarily on monocytes and macrophages and on endothelial cells. The end result is activation of the coagulation cascade, which leads to microvascular thrombus formation, organ dysfunction, and bleeding.
Several lines of evidence suggest that there is crosstalk between the inflammatory and coagulation cascades. For instance, TNF, IL-6, and IL-8 promote release of hyperreactive, ultralarge von Willebrand factor multimers from endothelial cells and inhibit the cleavage and clearance of these prothrombotic agents by metalloproteinases. Despite improved understanding of the coagulation pathway, it remains unclear why drotrecogin alfa improved survival in a phase 3 trial, whereas strategies targeted at other components of the coagulation cascade, such as tissue factor pathway inhibitor and antithrombin III, had no impact on mortality.

Immune Suppression

Of the patients who die from severe sepsis, only a few die shortly after the onset of sepsis, and these deaths are almost always due to profound refractory hypotension or hypoxemia. Many patients have a prolonged ICU course and often die following nosocomial infections. Experimental findings suggest a shift from T helper cell (Th1) response, where immune cells secrete proinflammatory cytokines, to Th2 response, where antiinflammatory cytokines, such as IL-4 and IL-10, predominate during the latter periods of severe sepsis. Another important finding is the reduced expression of Th1 cytokines, particularly TNF and interferon-γ, by monocytes in response to infectious stimuli in ex vivo studies. These changes in cell expression could represent a protective response against uncontrolled inflammation. Yet, these changes may place individuals at higher risk of hospital-acquired infections. Several terms have been proposed to describe these changes in immune cell function during infection and sepsis, such as endotoxin tolerance, anergy, immunodepression, and cellular reprogramming.

Apoptosis

Cells die in two ways, necrosis and apoptosis. During necrosis, the cell membrane is damaged and the necrotic tissue is degraded by phagocytic cells. In contrast, apoptosis or programmed cell death is a normal cellular process. Sepsis is accompanied by increased apoptosis of lymphoid cells and, to a lesser extent, parenchymal cells. Ingestion of apoptotic cells by macrophages may lead to a Th2 response, whereas ingestion of necrotic cells may lead to Th1 response. Therefore, apoptosis may contribute to immune suppression. Endogenous glucocorticoids, released during stress, increase apoptosis. Therapeutic strategies to block intracellular signaling leading to increased apoptosis in lymphoid cells are being studied as a potential treatment for sepsis.

Epithelial and Endothelial Dysfunction

Epithelial cell line organs are involved in MODS, including the liver, kidney, lung, and intestine. Increased permeability and loss of the epithelial cell barrier are therefore hypothesized to play an important role in MODS. For example, increased permeability of lung epithelial cells manifests clinically as acute lung injury or acute respiratory distress syndrome. The damage to gut barrier function leads to translocation of gram-negative bacteria in the systemic circulation. Epithelial dysfunction may occur because of the various mechanisms outlined previously, including increased apoptosis. In a murine model of Pseudomonas pneumonia-induced sepsis, the inhibition of gut epithelial apoptosis improved survival, suggesting that apoptosis in the intestinal epithelium may play an important role in sepsis.

Similar to the epithelial system, the endothelium system plays an important role in sepsis. The endothelium possesses anticoagulant and antithrombotic properties, and damage to the endothelium activates the coagulation cascade and increases nitric oxide, which may mediate peripheral vasodilatation, hypotension, tissue hypoperfusion, and increased permeability, all frequently observed during severe sepsis.

In addition to the mechanisms outlined here, the role of ischemia–reperfusion injury and oxidative stress has been intensely studied in severe sepsis. Although tremendous advances have been made in our understanding of sepsis, several key questions remain unanswered. For instance, the mechanism of organ dysfunction in sepsis is not known. There appears to be discordance between clinical and histological evidence of organ dysfunction in autopsy
studies. Cell death is uncommon in these studies, and organ dysfunction may occur because of cell hibernation. Another important question is the exact mechanism of death during sepsis. Although the severity of MODS often determines the likelihood of survival, patients often die despite successful management of organ failure with dialysis, ventilators, and vasopressors. Finally, it is increasingly recognized that sepsis is a heterogeneous disorder and that a set of mechanisms may predominate in an individual. The host response to infection varies based on the size and type of pathogen and host characteristics, such as age and genetic background. In the future, advances in proteomics and genetics may be used to understand the predominant pathophysiological abnormality in a patient and provide individualized therapy.

Clinical Diagnosis

To ensure rapid implementation of effective therapies, the prompt diagnosis of severe sepsis is critical. The initial presumptive diagnosis of sepsis and severe sepsis can be made in the presence of an infection and severe sepsis criteria. The diagnosis of infection does not require microbiological or radiographic evidence. Only a clinical suspicion of infection and organ failure is necessary. In these patients, the absence of hypotension but an elevated lactate level is often an indication of tissue hypoperfusion and should prompt early aggressive therapy. This clinical approach allows initiation of diagnostic steps, to identify a source of infection, and therapeutic steps, including early goal-directed therapy and antibiotics.

Treatment

The Surviving Sepsis Campaign guidelines for the diagnosis and management of severe sepsis and septic shock were last published in 2008. These guidelines are an excellent source for review.

Antimicrobial Therapy and Source Control

Treatment for severe sepsis and septic shock rests upon the triad of antimicrobial management, hemodynamic resuscitation, and source control. Selective and well-chosen antibiotics must be vigorously applied in a timely fashion, dosed appropriately based on pharmacodynamic principles, and discontinued without excessive duration so as not to promote the emergence of resistant microorganisms.

Observational studies have shown an association between delays in appropriate antibiotic treatment and risk of death. For example, a Medicare database study of 14,000 elderly patients hospitalized with community-acquired pneumonia showed an increased risk of death when appropriate antibiotics were delayed 8 hours or more after hospitalization. A similar observation was made for patients who developed ventilator-associated pneumonia, with a delay in antibiotics increasing the risk of death by 77 times. Effective antimicrobial administration within the first hour of documented hypotension in severe sepsis is associated with increased survival, and mortality increases with each hour delay in effective antimicrobial therapy.

Antimicrobial therapy can only be effective in the context of appropriate source control. The need for such source control may be overlooked initially in many infections commonly found in the ICU, such as pneumonia-associated bacterial empyema, abscess, and Clostridium difficile colitis. Source control can include removal of implanted or tunneled devices, open surgical or percutaneous drainage of infected fluids or abscesses, and surgical resection of infected tissues. Efforts to identify infections requiring invasive forms of source control frequently require rapid radiographic imaging or immediate surgical intervention without imaging. Surgical source control typically follows aggressive resuscitative efforts to minimize intraoperative morbidity and mortality. In some cases where infections are rapidly progressive, as seen in necrotizing soft tissue infections, optimal management may require simultaneous aggressive resuscitation and surgical intervention. Earlier surgical intervention has been shown to have a significant impact on outcome in certain rapidly progressive infections, such as necrotizing fasciitis. The need for source control should be identified as soon as possible, at minimum within the first 6 hours after diagnosis of severe sepsis. The
effectiveness of source control interventions should be reassessed within 12 to 36 hours following institution.

In approximately 20% to 30% of cases, the initial choice of antibiotics is incorrect, based on subsequent culture and sensitivity specimen results, underscoring the importance of optimal initial antimicrobial therapy. The risk of inappropriate antibiotic selection is increased when resistant microorganisms are not suspected or patients have received prior antibiotics. Should one empirically “choose poorly,” mortality increases by 50% to 100%, as shown in septic shock and nosocomial pneumonia. Initial broad antibiotic coverage followed by de-escalation to narrow antimicrobial coverage following the results of cultures will maximize appropriate antibiotic coverage of inciting pathogens in septic shock and minimize selection pressure toward resistant organisms.

Microorganism eradication is directly related to optimizing the antimicrobial dosing regimen based on pharmacodynamic principles. Several studies have demonstrated that suboptimal dosing of antibiotics is common in ICU patients with sepsis or septic shock because these conditions can substantially increase volumes of distribution and decrease clearance rates. Data are most well developed in reference to aminoglycosides but also exist for fluoroquinolones, β-lactams, and carbapenems. Failure to achieve targets on initial dosing has been associated with clinical failure. Early optimization of antimicrobial pharmacokinetics can improve outcome of patients with severe infection, including septic shock. In general, this is most easily achieved by initiating antibiotic therapy with high-end dosing regimens.

Carefully selecting antibiotics, choosing an appropriate dose, writing orders, mixing bags in the pharmacy, transporting drug to the patient’s bedside, obtaining vascular access for IV infusion, and having a nurse administer the agent are all steps that represent a complex process of care. Physicians tend to overlook the nuances in this process of care, and delays can occur at any point along this continuum.

HEMODYNAMIC RESUSCITATION

The purpose of aggressive, sustained hemodynamic support is to maximize both systemic blood flow and arterial pressure, thereby restoring the balance between oxygen delivery and oxygen consumption. Preserving a sufficient MAP is fundamental to ensuring adequate organ perfusion and function. Few data exist to guide selection of a target blood pressure. The MAP is a better reflection of the arterial pressure head, and 60 to 65 mm Hg has traditionally served as a goal for resuscitation in North America. One study comparing MAPs of 65 mm Hg and 85 mm Hg found no difference in organ perfusion indices.

A single-institution clinical trial of 263 patients with severe sepsis or septic shock by Rivers and colleagues examined the hypothesis that early, protocolized, goal-directed resuscitation improves survival. This study examined goal-directed resuscitation and determined it to be an effective approach when initiated within the first 6 hours in the emergency department and well prior to ICU admission, as opposed to the previous studies that targeted later ICU care. A delay in resuscitation may prevent reversal of tissue injury from occult ischemia. The intervention arm used protocolized care whereby fluid boluses were given based on central venous pressure to optimize preload, vasopressor therapy was started to improve MAP (>65 mm Hg), and packed red blood cells were transfused and dobutamine infusions used to improve oxygen delivery if mixed venous oxygen saturation remained less than 70%. The control group received conventional monitoring, with mostly back-loaded resuscitation in the ICU. Patients randomized to the protocolized, goal-directed approach had a significant decrease in mortality and morbidity (30.5% in the early goal-directed therapy group vs 46.5% in the control group, P = 0.009). A larger multicenter study to confirm findings of this single center study is underway.

The initiation of vasopressor support depends on the patient’s clinical status following fluid resuscitation. Vasopressor support is indicated if hypotension is associated with evidence of tissue or organ hypoperfusion, including oliguria, obtundation, and lactic acidosis. The choice of vasopressor is based on its efficacy to improve
blood pressure and adverse effect profile. Norepinephrine and dopamine are recommended as first-line drugs, with more recent data suggesting that norepinephrine is preferred in most patients. Norepinephrine may have more powerful vasopressor activity than dopamine. It is expected to increase cardiac output but not as much as dopamine. Excessive tachycardia is more likely to occur with dopamine. In addition, dopamine can exert significant immunosuppressive effects through suppression of prolactin production from the hypothalamus. Studies comparing the effects of norepinephrine and dopamine on renal and splanchnic perfusion have had mixed results, and neither agent has demonstrated conclusive superiority. Although early studies suggested that low-dose dopamine can prevent renal dysfunction, a subsequent randomized controlled trial did not confirm these findings. Choosing a vasopressor will by necessity remain somewhat of an art. For example, despite a general preference for norepinephrine, if a patient with septic shock has relative bradycardia and known low cardiac output despite adequate volume resuscitation, then dopamine is likely the better choice.

Epinephrine, the most potent adrenergic agent available, has been demonstrated in some studies to disproportionately decrease splanchnic blood flow, gastric mucosal pH, and splanchnic oxygen consumption as well as increase blood lactate in septic patients. A prospective randomized trial compared mortality using norepinephrine and dobutamine with epinephrine in 330 subjects with septic shock. The trial was designed to assess large differences in mortality. Subjects who received epinephrine had slightly higher mortality (40% vs 34%, P = 0.31). Lactic acidosis was more common in the subjects who received epinephrine.

Phenylephrine, a pure vasoconstrictor, is generally avoided unless cardiac output is high or other vasopressors have produced arrhythmias. It is a relatively pure α-adrenergic agonist, has minimal or absent inotropic effects, and tends to cause reflex bradycardia. For that reason, it can be very useful in the context of excessive tachycardia or concurrent tachyarrhythmias.

Vasopressin acts on vascular smooth muscle, independent of adrenergic receptors, by binding to V1 receptors. The availability of a nonadrenergic vasopressor is attractive, because septic shock is typified by downregulation of adrenergic responsiveness. Moreover, the posterior pituitary gland becomes rapidly depleted of native vasopressin with prolonged shock, leading to a hormonal deficiency. However, the Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock (VASST) trial, a multicenter, randomized, double-blind study to compare vasopressin (0.01-0.03 U/min) to norepinephrine (5-15 μg/kg/min) in patients with septic shock, showed no difference in 28-day mortality.

**Corticosteroids**

The use of corticosteroids to treat septic shock remains controversial. Although early clinical trials and animal studies initially supported the use of high doses of corticosteroids for a short duration, they ultimately were associated with worse outcomes in randomized clinical trials. Whether low-dose steroids improve survival in septic shock remains controversial.

Sepsis may be associated with relative adrenal insufficiency in a substantial subset of patients. Among other deleterious effects, impairment of catecholamine sensitivity can result from adrenal insufficiency. Several studies have demonstrated that administration of low- or stress-dose steroids (200-300 mg hydrocortisone daily equivalent) to patients with septic shock can decrease vasopressor requirements and suppress inflammatory markers. Annane and colleagues performed a short adrenocorticotropic hormone (ACTH) stimulation test and discovered that 54% of their 189 patients in septic shock were nonresponders. Patients with relative adrenal insufficiency and nonresponders did not experience increased cortisol levels (<9 μg/dL). Given evidence that the severely septic host could be adrenally insufficient, it was hypothesized that corticosteroids might be instrumental in reversing circulatory shock and improving survival. In small, single-institution, randomized studies, patients with septic shock received either 100 mg IV hydrocortisone 3 times daily or a placebo. The investigators demonstrated faster
reversal of shock in subjects who received hydrocortisone and a trend toward improved survival.

In a prospective, randomized multicenter trial of 299 French men and women in septic shock, patients underwent an ACTH stimulation test and then received hydrocortisone (50-mg IV bolus 4 times daily) and fludrocortisone (50-mg oral dose once daily) for 7 days. Remarkably, approximately 70% of the patients were found to be adrenal insufficient. Corticosteroid therapy decreased 28-day mortality by 10% in ACTH nonresponders. There was no benefit for corticosteroid administration in patients who successfully responded to the ACTH challenge.

The Corticosteroid Therapy for Septic Shock (CORTICUS) trial, a randomized multicenter study, examined the role of low-dose hydrocortisone (200 mg/d IV) in septic shock. No difference in 28-day mortality was observed among patients who did and did not receive hydrocortisone (34.3% in the hydrocortisone group and 31.5% in the placebo group, \( P = 0.51 \)). Furthermore, there was no difference in survival in subgroups who were responders or nonresponders according to results of the ACTH stimulation test. The proportion of patients in whom shock was reversed was similar among those who did and did not receive hydrocortisone, but shock reversal was faster in the group who received hydrocortisone.

The conflicting results of these trials may have occurred for several reasons. First, patients enrolled in the Annane trial were sicker than those enrolled in the CORTICUS trial. In the Annane trial, entry criteria included persistent hypotension despite fluid resuscitation and vasopressors (blood pressure unresponsive to vasopressors), whereas in the CORTICUS trial, the entry criterion was vasopressor requirement following fluid resuscitation (most had blood pressures responsive to vasopressors). Second, patients were enrolled in the Annane trial within 3 hours of the onset of shock, whereas patients could be enrolled up to 72 hours after the onset of shock in the CORTICUS trial. Therefore, low-dose hydrocortisone is most likely to benefit patients with shock that is not responsive to vasopressors. Furthermore, there is no evidence to support use of hydrocortisone to treat severe sepsis in the absence of shock.

Additionally, there is significant variability in the results of cortisol assays among research centers and between a research center and the reference laboratory source. Finally, it is possible that the free cortisol level is the primary determinant of a response to steroids and that all the data published to date concern total cortisol assays. Free and total cortisol levels may vary significantly based on serum protein concentration. These observations and the results of the CORTICUS study suggest that results of ACTH stimulation tests should not guide the decision to administer low-dose hydrocortisone in septic shock. There is consensus that regardless of any beneficial clinical outcome effect of steroids in septic shock, shock (defined as vasopressor requirement) is reversed sooner in patients receiving steroids. Steroids may be considered in fluid-resuscitated patients with hypotension that is poorly responsive to vasopressors.

**Drotrecogin Alfa**

The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial demonstrated a 6.1% absolute decrease in mortality (30.8% vs 24.7%, \( P = 0.005 \)) in patients with severe sepsis. Recombinant activated protein C (rhAPC) was approved by the US Food and Drug Administration for use in patients with sepsis-induced organ dysfunction associated with a high risk of death, such as an Acute Physiology and Chronic Health Evaluation II score of 25 or more or multiple organ failure.

Several additional studies have been conducted to assess the efficacy of rhAPC in less severely ill patients and the pediatric population. The Extended Evaluation of Recombinant Human Activated Protein C (ENHANCE) trial revealed a somewhat greater incidence of serious hemorrhage with rhAPC than was evident in the PROWESS trial. The Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis (ADDRESS) trial examined the effect of rhAPC in patients with severe sepsis at low risk of death and supported the Food and
Drug Administration labeling that rhAPC was not of utility in such patients. The pediatric trial also failed to show efficacy.

Clinicians should consider the risk of bleeding, particularly intracranial hemorrhage, when deciding whether to administer rhAPC. A large multicenter trial to determine efficacy of activated protein C in patients with septic shock is underway, and results should be available shortly.

**Glucose Control**

Hyperglycemia and insulin resistance are common in sepsis. In 2001, Van den Berghe and colleagues demonstrated that intensive insulin infusions titrated to strict glycemic control in critically ill surgical patients could be beneficial. These investigators tested an intensive insulin protocol titrated to a blood glucose of 80 to 110 mg/dL against conventional treatment in more than 1,500 critically ill surgical patients. Subjects in the latter group received infusion of insulin only if their blood glucose level exceeded 215 mg/dL and then received maintenance of glucose at a level between 180 and 200 mg/dL. Most patients (62%) had undergone cardiac surgery. The experimental group received a continuous infusion of insulin, titrated according to frequent blood glucose testing. The mean daily dose of insulin was more than double that given to the control patients (71 vs 33 U/h, P < 0.001). The mean blood glucose in the experimental group was 103 mg/dL and that in the control group was 153 mg/dL. The patients randomized to intensive insulin therapy experienced a mortality reduction of 50%, with fewer septic episodes, fewer instances of bacteremia, fewer cases of multiple organ failure, fewer instances of critical illness polyneuropathy, less time on artificial support such as mechanical ventilation and hemodialysis, and fewer transfusions.

A second study by Van den Berghe targeted medical ICU patients and used the same strict upper threshold target of 80 to 110 mg/dL. In the intention-to-treat analysis, there was no difference in mortality (40% in the conventional treatment group vs 37.3% in the intensive treatment group, P = 0.33). Morbidity was lower in the intensive insulin therapy group, as evidenced by lower incidence of acute kidney injury and earlier weaning from mechanical ventilation. The investigators also reported hypoglycemia in 5.2% in the intensive insulin group compared with 0.8% in the control group.

A multicenter randomized trial in Germany examined the role of intensive insulin therapy using a similar insulin protocol. The trial was stopped early (n = 537) because of a high incidence of hypoglycemia, defined as blood glucose 40 mg/dL or less (17.0% vs 4.1%, P < 0.001). No difference was observed in 28-day mortality. Another multicenter trial, the GIUCO control trial in Belgium, has been reported in abstract form only. This trial, after recruiting approximately 500 subjects, was also stopped early because of a high incidence of hypoglycemia. No difference in mortality was observed. It is important to emphasize that despite higher incidence of hypoglycemia, these trials may be underpowered to assess differences in survival. Whether less strict glycemic control targeting blood sugar of approximately 150 mg/dL would be more likely to improve mortality without causing life-threatening hypoglycemia is not known.

The Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) was a multicenter, multinational randomized clinical trial involving 6,100 subjects from 42 hospitals in Australia, New Zealand, Canada, and the United States. The NICE-SUGAR investigators compared conventional therapy (maintaining the glucose concentration at ≤180 mg/dL) to a regimen of intensive glucose control with a target glucose of 81 to 108 mg/dL. The primary outcome, 90-day mortality, was higher in the intensive glucose control group (27.5% vs 24.9%, P = 0.02). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (odds ratios for death in the intensive control group, 1.31 and 1.07, respectively; P = 0.10). Severe hypoglycemia (blood glucose level ≤40 mg/dL) was reported in 206 of 3,016 patients (6.8%) in the intensive control group and 15 of 3,014 (0.5%) in the conventional control group (P < 0.001). The higher mortality in the intensive glucose control group occurred despite a much lower rate of
hypoglycemia than reported in any previous studies of combined surgical and medical patients. It is important to emphasize that the findings of NICE-SUGAR do not justify neglecting glycemic control. Rather, a glucose level higher than 180 mg/dL should be treated, targeting a blood glucose concentration between 120 and 180 mg/dL.

**Other Support Modalities**

Indications for acute dialysis in the ICU population are not dissimilar to those for other patients. These indications include volume overload, electrolyte imbalance, acid-base disturbances, elevated blood urea nitrogen, uremic pericarditis, and uremic encephalopathy. Unfortunately, ICU patients, especially those with acute renal failure, may have altered hemodialysis kinetics, such that standard intermittent dialysis may offer suboptimal urea clearance kinetics, despite apparently equivalent doses. Compared with standard intermittent dialysis, daily hemodialysis has been shown to yield higher urea clearance and may be necessary in patients with severe sepsis.

The Veterans Administration/National Institutes of Health Acute Renal Failure Trial network compared different intensities of dialysis for acute kidney injury in patients with severe sepsis. The intensive treatment strategy included intermittent hemodialysis, sustained low-efficiency dialysis (SLED) 6 times per week, or continuous venovenous hemofiltration at 35 mL/kg of body weight per hour. The less-intensive treatment strategy provided intermittent hemodialysis, SLED three times weekly, or continuous venovenous hemofiltration at 20 mL/kg per hour. No differences in mortality, recovery of kidney function, or other organ failures were observed.

Recent meta-analyses suggest that early enteral feeding lowers risk of infection and improves survival compared with delayed feeding in the critically ill. These findings are consistent with animal studies demonstrating that enteral nutrition maintains gut mucosal integrity, decreases bacterial translocation, and limits the SIRS to bacterial toxins. The amount of nutritional support patients should receive and the role of glutamine, arginine, and omega fatty acids remain unclear. Studies of parenteral feeding in the ICU have failed in general to demonstrate an improvement in mortality in critically ill patients. Other studies demonstrate the superiority of enteral over parenteral feeding in critically ill patients, with respect to costs and complications, including risk of infection.

**LONG-TERM OUTCOMES**

The traditional focus of care in patients with infectious disease has been to reduce short-term mortality, and clinical trials have used 28-day or 90-day mortality as an end point. However, recent studies suggest that infection may worsen long-term outcomes. Although it is commonly believed that serious infection occurs in older subjects with chronic health conditions and that these conditions contribute to higher mortality even after recovery from acute illness, several studies show that higher long-term mortality is independent of baseline functional and health status. These studies suggest that pathophysiological processes initiated during infection may lead to higher long-term mortality. For instance, recent studies suggest that the immune response activated during an acute infection can remain upregulated during recovery and is associated with higher long-term mortality, particularly that due to cardiovascular disease. Higher circulating levels of inflammatory and coagulation markers were observed at hospital discharge when patients appeared to have clinically recovered from infection, and these markers were associated with increased subsequent mortality.

Adverse long-term outcomes are not limited to increased mortality risk. Acute infections can worsen chronic diseases, and the relationship between acute infection and chronic illness is bidirectional. Whereas the increased burden of chronic health conditions increases the risk of infection and sepsis, survivors of infection may develop a higher burden of chronic disease. For example, individuals with renal disease are at higher risk for serious infection. The episode of serious infection can lead to renal failure and eventually chronic dialysis. Similarly, it has been shown that infection with influenza is associated with increased risk of cardiovascular disease. These examples underscore the complex relationship between infection and underlying...
chronic disease, where comorbid conditions are a risk factor and are modified by the infectious event. The worsening of chronic illness following infection is in turn a risk factor for subsequent acute illness, thereby initiating a spiral of events that can ultimately lead to death.

**SUMMARY**

Morbidity and mortality from severe sepsis and septic shock remain high. Early identification of patients with severe sepsis, in particular sepsis-induced tissue hypoperfusion, is a high priority. The protocolized approach to identification and management of patients with severe sepsis is crucial. Providing performance feedback as part of a quality assurance program is the best way to change how health care practitioners treat severe sepsis.

**REFERENCES**


