The Management of Severe Sepsis and Septic Shock

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Severe sepsis and septic shock persist as major health care problems despite ongoing research to improve overall outcomes. Overall mortality from severe sepsis or septic shock ranges from 30% to 60% despite aggressive medical care and accounts for 9.3% of all deaths in the United States.1–3 In fact, severe sepsis and septic shock is the 10th leading cause of death in the United States.4 More than 750,000 cases of sepsis occur each year in the United States, resulting in more than 380,000 intensive care admissions and initiation of mechanical ventilation in 130,000 cases. The number of cases of severe sepsis and septic shock has been estimated to reach 934,000 and 1,110,000 cases by the years 2010 and 2020. Severe sepsis and septic shock also consume considerable health care resources with the average cost per case being $22,000. Annual total costs associated with the care of patients who have sepsis have been estimated to be near $17 billion.1 These annual costs will most likely increase in the upcoming years because of the overall aging population, emergence of newer antimicrobial-resistant bacteria, and increasing use of invasive therapeutic measures.

Sepsis is defined by a systemic inflammatory response syndrome, such as fever, tachypnea, tachycardia, or leukocytosis, in response to a culture-proven or clinically suspected infection. The clinically suspected infections may include a wound with purulent discharge, community-acquired pneumonia in a previously healthy individual, or ruptured bowel with free air or bowel contents in the peritoneum. More recently the grading system of sepsis was modified to include severe sepsis, septic shock, and refractory septic shock.3,5 Severe sepsis includes the previously mentioned clinical criteria for sepsis in addition to at least one sign of organ hypoperfusion or

KEYWORDS
- Severe sepsis
- Septic shock
- Goal-directed therapy
- Empiric antibiotics
- Vasoactive agents
- Biomarkers
dysfunction, such as cardiac dysfunction, acute lung injury, or altered mental status. Septic shock is defined by severe sepsis in addition to a systemic mean blood pressure less than 60 mm Hg (or <80 mm Hg if previous hypertension) after an attempt at adequate fluid resuscitation or a need for vasopressors to maintain a systemic mean blood pressure greater than 60 mm Hg (or >80 mm Hg if previous hypertension). Finally, refractory septic shock exists if dopamine greater than 15 \( \mu g/kg/min \) or norepinephrine or epinephrine greater than 0.25 \( \mu g/kg/min \) is required to maintain a mean blood pressure greater than 60 mm Hg (80 mm Hg if previous hypertension). These definitions were established to facilitate early diagnosis, follow physiologic responses, aide entry into clinical trials, and help staging and prognostication.

The occurrence of septic shock seems to peak in the sixth decade of life. Predisposing factors include male sex, non-white ethnic origin in North Americans, comorbid diseases, malignancy, immunodeficiency or immunocompromised state, chronic organ failure, alcohol dependence, and genetic factors. The most common sites of infection include the respiratory tract, genitourinary system, and abdomen. In 25% of individuals who have severe sepsis or septic shock, multiple sites of infection can account for the clinical presentation. Twenty percent of individuals have severe sepsis or septic shock with site unknown.

The causative organism of severe sepsis and septic shock depends on multiple factors, including endemic microbial pathogens (eg, malaria in Southeast Asia), patient comorbid conditions (HIV, malignancy), and possible microbial colonization. Gram-positive bacteria account for most pathogens associated with severe sepsis and septic shock with a range of 30% to 50%. Severe sepsis and septic shock due to gram-negative bacteria have been diminishing, but still account for 25% to 30% of cases, with a higher prevalence in genitourinary infections. Over the past decade, the percentage of multidrug-resistant (MDR) bacteria has significantly increased. In addition, the number of cases of severe sepsis or septic shock due to fungi has also significantly increased. In fact, MDR bacteria and fungi account for 25% of cases of severe sepsis and septic shock. Viruses and parasites are identified in 2% to 4% of cases; however, this may be an underestimate. In 20% to 30% of cases, a causative organism is not identified, which may be affected by the relatively low sensitivity of blood cultures and preadministration of antibiotics.

**INITIAL ASSESSMENT**

Sepsis is the result of complex interactions between the infecting microorganism and host immune, inflammatory, and coagulation responses. Sepsis has been divided into phases, early and late, by fluctuations in these specific host responses and to facilitate further targeted therapies. The early stage of sepsis, defined as the first 6 hours, is highlighted by an early diagnosis of severe sepsis or septic shock and institution of early, goal-directed therapy. Early goal-directed therapy allows for ongoing patient assessment and results in a decrease in both in-hospital and overall mortality. Many critical first-line therapies should be administered during this crucial period in severe sepsis and septic shock (Fig. 1).

The first priority in a patient who has severe sepsis or septic shock involves stabilization of the airway and breathing. Supplemental oxygen should be provided to the patient and institution of mechanical ventilation should be performed if necessary. Second, an assessment of perfusion should be performed. Blood pressure should be assessed by a sphygmomanometer or arterial catheter if blood pressure is labile. However, attempts at placing an arterial line to obtain an accurate assessment of blood pressure should not delay further management of severe sepsis or septic shock.
Once hypoperfusion is documented, early restoration of perfusion is necessary to limit secondary organ dysfunction and reduce mortality (Fig. 2). Goals of initial resuscitation of sepsis-induced hypoperfusion should include: (1) Central venous pressure of 8 to 12 mm Hg. If a patient is mechanically ventilated, a higher central venous pressure of 10 to 12 mm Hg is recommended. The mean arterial pressure (MAP) should be maintained at 60 mm Hg or higher. The systolic blood pressure (SBP) should be equal to or greater than 90 mm Hg.

**Initial resuscitation complete**

- **GOALS**
  - SBP ≥90 mm Hg
  - MAP ≥60 mm Hg
  - CVP ≥8 mm Hg
  - ScvO2 ≥70%

**All goals achieved**

- Transfuse if hematocrit <30%
- Begin inotrope if low CI suspected

**Initial fluid bolus of ≥1000mL crystalloid or ≥500mL colloid**

- **SBP <90 mm Hg**
  - MAP <60 mm Hg
  - CVP <8 mm Hg
  - Measure CVP

- **CVP ≥8 mm Hg**
  - Measure BP
  - SBP <90 mm Hg
  - MAP <90 mm Hg

- **ScvO2 <70%**

- **Measure ScvO2**

- **Start vasoactive agents**

- **Begin vasoactive agents**

- **Consider source control**

**Overall Management of Severe Sepsis and Septic Shock**

- **First Line**
  - Stabilize airway
  - Assess perfusion
  - Begin goal-directed fluid resuscitation
  - Initiate vasoactive agents (if needed)
  - Place central venous catheter and arterial canula (if needed)
  - Obtain antimicrobial cultures
  - Administer empiric appropriate antibiotics
  - Consider source control

- **Second Line**
  - Institute corticosteroids if appropriate
  - Assess need for activated protein C
  - Initiate intravenous insulin for hyperglycemia
  - Administer blood products for anemia
  - Institute lung-protective ventilation strategies
  - Evaluate for nutrition
  - Initiate prophylactic measures (e.g. for venous thromboembolism and gastrointestinal hemorrhage)

**Fig. 1.** Therapies used in the treatment of severe sepsis and septic shock.

**Fig. 2.** Initial resuscitation with goal-directed therapy in the initial stage of severe sepsis and septic shock. CVP, central venous pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; ScvO2, central venous oxygen saturation.
pressure target of 12 to 15 mm Hg is recommended to account for the filling impediment;13 (2) Mean arterial pressure 65 mm Hg or greater; (3) Urine output 0.5 mL/kg/h or more; (4) Central venous or mixed venous oxygen saturation greater than or equal to 70% or greater than or equal to 65%, respectively.11 This initial volume resuscitation should be performed with either 1000 mL or more of crystalloid (0.9% sodium chloride/normal saline or lactated Ringer solution) or 300 to 500 mL of colloids (5% albumin or 6% hydroxyethyl starch) over 30 minutes. There is no difference in outcomes when colloid or crystalloid is used for resuscitative efforts; however, hydroxyethyl starch has been associated with reports of renal failure and increased bleeding.14–16 Volume status, tissue perfusion, and blood pressure must be assessed after the initial fluid challenge and further fluid administration should be continued as long as the hemodynamic improvement continues or until the previous goals are met. Large fluid deficits exist in patients who have severe sepsis or septic shock and up to 6 to 10 L of crystalloid or 2 to 4 L of colloid may be required for resuscitation in the first 24 hours.10 If the goals for central venous or mixed venous oxygen saturations are not met during the initial 6 hours, consideration can be given to transfusing red blood cells to achieve a hematocrit greater than or equal to 30% or administration of a dobutamine infusion.10,11 Finally, in the setting of life-threatening hypotension, vasoactive agents may be required for supportive care during the initial fluid resuscitation stage.

DIAGNOSIS

Appropriate antimicrobial cultures should be obtained on initial presentation of severe sepsis or septic shock. At least two blood cultures should be obtained with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently placed within the last 48 hours.11 Cultures from other sites that may be the source of infection, such as urine and sputum, should be also obtained. Although obtaining these cultures is essential to confirm infection and allow tapering of antibiotic regimens, they should not delay the administration of early and appropriate antibiotics.

ANTIBIOTIC THERAPY

Multiple studies have documented the critical nature of early administration of broad-spectrum antibiotics and the effect on mortality (Fig. 3).17–19 In a recent retrospective cohort study in patients who had septic shock, increasing delays in the initiation of effective antimicrobial therapy after the onset of hypotension were associated with

![Fig. 3. Effects of inappropriate and appropriate antimicrobial therapy on mortality in severe sepsis and septic shock. (Data from references 24, 78–82)](image-url)
a significantly increased risk for death. The median time to initiation of effective therapy was also shown to be a significant predictor of mortality.10 The most recent guidelines from the Surviving Sepsis Campaign recommend starting intravenous antibiotic therapy as early as possible because each hour delay in administration of effective antibiotics is associated with a measurable increase in mortality.11,17,20 The initial selection of antimicrobial therapy should be broad enough to cover all likely pathogens and be able to penetrate in adequate concentrations into the presumed source of sepsis (Fig. 4). In areas with a relatively high prevalence of Candida species, an echinocandin to cover fluconazole-resistant Candida glabrata and krusei should be included in the antimicrobial milieu for presumed fungal sepsis.17,23 Patient factors, such as recent antibiotic administration, underlying comorbid conditions, risk factors for colonization with MDR pathogens, and documented drug intolerances also play a crucial role in initial selection of antibiotic therapy. Initial treatment of presumed MDR pathogens as a source of severe sepsis and septic shock should include combination therapy with two antimicrobial agents to increase the likelihood of providing appropriate treatment and resultant improved mortality.24 In locations with MDR pathogens, such as Klebsiella pneumoniae carbapenemase (KPC) gram-negative bacteria, and pan-resistant Pseudomonas aeruginosa, antimicrobial treatment with alternative regimens, such as colistin, should be considered. Knowledge of local susceptibilities and pathogen minimum inhibitory concentration (MIC) is also critical when selecting the initial antimicrobial regimen. One recent study found that empiric therapy with piperacillin-tazobactam for treatment of pseudomonas bacteremia with reduced susceptibility was associated with increased mortality, despite being appropriate.25 If high MICs to cefepime and piperacillin-tazobactam are prevalent, broader coverage with

![Fig. 4. Initial antibiotic selection for severe sepsis and septic shock.](image-url)
a carbapenem may be more appropriate rather than use of inferior therapies. Consideration can also be given to different antimicrobial dosing strategies, such as continuous infusion, to maximize the time above the MIC for treatment of causative pathogens.26

Patients who have severe sepsis or septic shock warrant broad-spectrum therapy until the causative organism is identified. Once culture results and antimicrobial susceptibility data return, further therapy should be pathogen directed and all unnecessary antibiotics should be discontinued in accordance with good antimicrobial stewardship to avoid drug toxicities and the development of nosocomial superinfections with *Candida* species, *Clostridium difficile*, or vancomycin-resistant enterococcus.27 Such de-escalation approaches in patients who have severe sepsis and septic shock have been shown to have improved outcomes.28 The duration of antibiotic therapy is somewhat controversial; however, current recommendations are to continue therapy for 7 to 10 days. Longer courses of therapy may be appropriate in patients who have a slow clinical response, undraining focus of infection, or immunologic deficiencies, such as neutropenia.11 In most cases of severe sepsis or septic shock, antimicrobial cultures are negative and thus the decision to continue, taper, or stop antibiotic therapy must be made on the basis of clinical information.6,8

**CATHETERS**

Frequently in severe sepsis and septic shock, blood pressure readings from a noninvasive arm cuff are inaccurate. Systolic pressure with an arm cuff often overreads at low pressures (<60 mm Hg) and the use of an arterial cannula provides a more accurate and reproducible measurement of true arterial pressure. In addition, an indwelling arterial cannula provides continuous analysis so that decisions regarding therapy can be based on immediate and accurate information. Vasoactive agents are required once fluid resuscitation does not restore adequate hemodynamic function. These agents should be administered through a central venous catheter as soon as one is available. Once appropriately placed with the tip of the catheter at the cavoatrial junction, frequent assessments of the central venous pressure and mixed venous oxygen saturation can be obtained to assist in volume resuscitation efforts in the early stages of septic shock. Often in severe sepsis and septic shock, empiric antibiotics are given during the early phases of volume resuscitation/vasopressor initiation and multiple venous accesses are required. Placement of a multilumen catheter can alleviate this potential problem. Use of pulmonary artery catheters has declined over the past 2 decades due to the lack of a definitive benefit.29 Pulmonary artery catheters can provide potentially useful information, such as an assessment of cardiac function in patients who have severe sepsis and septic shock; however these advantages are plagued by results that are subject to interpretation and may not reflect the true hemodynamic status.30 Although pulmonary artery catheter insertion may be appropriate in select cases, the routine use of pulmonary artery catheters in patients who have severe sepsis or septic shock is not recommended.

**VASOACTIVE THERAPY**

Vaspressors and inotropes are used when volume expansion alone is not able to restore adequate hemodynamic function or during fluid resuscitation in the setting of life-threatening hypotension. Vaspressors differ from inotropes, which increase cardiac contractility; however, many drugs have both vasopressor and inotropic effects. Potential agents include dopamine, norepinephrine, phenylephrine, epinephrine, and vasopressin. Using these therapies, the mean arterial pressure (MAP) should
be maintained at 65 mm Hg or greater, because this has been shown to preserve
tissue perfusion in severe sepsis and septic shock. Currently, there is no definitive
evidence of the superiority of one vasopressor over another toward patient-oriented
outcomes. The choice of vasopressor should depend on the desired physiologic
effect, subsequent response, and possible adverse effects.

Norepinephrine is a strong α-adrenergic agonist with less pronounced β-adrenergic
effects; as a result, a significant increase in MAP and systemic vascular resistance,
with little change in cardiac rate or output, is observed. Because of its potent vaso-
constrictive activity, it is commonly used as an initial vasoactive agent in severe sepsis
and septic shock. Dopamine is a natural precursor of norepinephrine and epinephrine
and possesses distinct dose-dependent pharmacologic effects. At lower doses, it
acts on dopaminergic receptors resulting in selective vasodilatation in renal mesen-
teric and coronary beds. Further increases in the dose result in stimulation of
β1-adrenergic receptors resulting in an increase in heart rate and cardiac contractility.
At higher doses, α1-adrenergic effects predominate, leading to arterial vasoconstriction.
Low-dose dopamine should not be used to preserve renal function because
there is no difference in urine output, need for renal replacement, or survival compared
with placebo. Dopamine is also more arrhythmogenic and should be used with
cautions in patients who have underlying heart disease. Epinephrine has potent β1-
adrenergic and moderate β2- and α1-adrenergic effects. Increases in cardiac output
result at lower doses with vasoconstriction predominating at higher doses. The degree
of splanchnic vasoconstriction and risk for dysrhythmias seems to be greater with
epinephrine compared with other vasoactive agents. Phenylephrine has purely
α-adrenergic agonist activity and results in vasoconstriction with minimal cardiac
inotropy or chronotropy. As a result, phenylephrine may be a good choice when tachy-
arrhythmias limit therapy with other vasopressors.

Recent studies have shown that vasopressin levels in septic shock are lower than
anticipated for a shock state, which may contribute to persistent hypotension. Current evidence documents the efficacy of adding low-dose vasopressin in severe
sepsis and septic shock that is refractory to other vasopressors. A recent study,
however, failed to show any benefit on mortality when used in combination with
norepinephrine. Potential complications from vasopressin infusion include coronary
and mesenteric ischemia.

Dobutamine is not a vasopressor but is an inotrope that has variable effects on blood
pressure. Primarily it has both β1- and β2-adrenergic effects resulting in an increase in
heart rate and cardiac contractility. Dobutamine should be considered for patients who
have low cardiac output in the presence of adequate left ventricular filling pressure and
adequate mean arterial pressure. Other vasopressors, such as dopamine, norepi-
 nephrine, and epinephrine, also have inotropic effects in addition to their vasoconstric-
tive effects. An inotrope should be considered to maintain an adequate cardiac index,
mean arterial pressure, mixed venous oxygen content, and urine output.

**SOURCE CONTROL**

Eradication of the inciting infection is essential to the successful treatment of severe
sepsis and septic shock. Source control represents a key component of success
and involves the drainage of infected fluids, removal of infected devices, debridement
of infected soft tissues, and definitive measures to correct anatomic derangement
resulting in ongoing antimicrobial contamination. Every patient presenting with
severe sepsis or septic shock should be evaluated as soon as possible for the pres-
ence of a focus of infection amenable to source control measures. These
infectious foci should be controlled with the least physiologic upset possible (eg, percutaneous rather than surgical drainage of an abscess) because certain source control interventions may cause further complications. If intravascular access devices are believed to be a possible source of severe sepsis or septic shock, they should be removed as soon as possible. The risks and benefits of the specific intervention plus the risks of transfer should be evaluated on an individualized basis.43

CORTICOSTEROIDS

The role of corticosteroids in the treatment of severe sepsis and septic shock has been controversial. The therapeutic role of corticosteroids arose from the theory that severe sepsis or septic shock results from an exaggerated and uncontrolled host inflammatory response. Another theory suggested that critically ill patients can suffer from a relative adrenal insufficiency. Early randomized controlled studies documented a decrease in the time to shock resolution; however, a reduction in overall mortality was not observed with high-dose corticosteroids.44,45 Further studies using lower, more physiologic doses of steroids further documented a reduction in the time of shock reversal and cessation of vasopressor use.46 A subsequent larger multicenter randomized controlled trial of patients who had vasopressor-unresponsive septic shock showed a reduction in mortality rate in all patients with a further reduction in time to shock resolution in patients who had relative adrenal insufficiency as defined by a suboptimal adrenocorticotropic hormone (ACTH) cortisol response.47 The Corticosteroid Therapy of Septic Shock (CORTICUS) trial, a large multicenter trial in which patients who had septic shock were randomized to either hydrocortisone or placebo, showed a faster reversal of shock among all patients.48 The trial failed to show a mortality benefit with steroid therapy, and in fact showed an increased incidence of superinfections, including new episodes of sepsis or septic shock.

Current recommendations from the Surviving Sepsis Campaign advocate that steroids should only be used in the setting of septic shock if a patient’s blood pressure is poorly responsive to both adequate fluid resuscitation and vasopressor support.11 An ACTH stimulation test has been used early in the course of sepsis to identify those patients who have a relative adrenal insufficiency who should then receive supplemental steroids. In the CORTICUS trial, however, the overall population of patients seemed to benefit regardless of ACTH stimulation test outcome.48 As a result, the ACTH stimulation test is no longer recommended to identify those patients who should receive steroids.11,49 Hydrocortisone should be used preferentially over dexamethasone because of a possible prolonged suppression of the hypothalamic-pituitary-adrenal axis after administration of dexamethasone.50 Doses of corticosteroids comparable to 200 to 300 mg/d of hydrocortisone should be used for the purpose of treating septic shock; however, there is no consensus regarding the duration and method of cessation (abrupt versus tapering) of steroids. Cessation of steroid administration should be considered when vasopressors are no longer required for the treatment of severe sepsis and septic shock.

RECOMBINANT ACTIVATED PROTEIN C

Activated protein C is an endogenous protein that is associated with fibrinolysis and the inhibition of coagulation and inflammation. Activated protein C inactivates factors Va and VIIIa, preventing the generation of thrombin, which inhibits platelet activation, neutrophil recruitment, and mast cell degranulation.9 During severe sepsis, the activation of protein C is inhibited by inflammatory cytokines and decreased levels of activated protein C have been associated with an increased risk for death.51 In a recent
study evaluating the efficacy of recombinant human-activated protein C (RHAPC) in severe sepsis, patients were randomized to receive either RHAPC or placebo. Premature cessation of the study occurred before completion because of the significant mortality benefit from RHAPC, although treated patients did have a higher bleeding diathesis. A subsequent open-label trial documented similar improvements in mortality, especially when RHAPC is administered within the first 24 hours of severe sepsis. Finally, a randomized placebo-controlled trail evaluating the efficacy of RHAPC in patients who had severe sepsis with a low risk for death as defined by an Acute Physiology and Chronic Health Evaluation (APACHE II) score less than 25 was terminated early because of the lack of any mortality benefit. This study also documented an increase in serious bleeding episodes in those patients treated with RHAPC. After compiling the results of the previously mentioned trials, RHAPC should be considered in patients who have severe sepsis with a high risk for death as defined by an APACHE II score of 25 or greater or multiorgan failure, if there are no contraindications, such as recent surgery, intracranial hemorrhage, or previous risk for bleeding. RHAPC is not recommended for patients who have severe sepsis and low risk for death.

INTRAVENOUS INSULIN

Hyperglycemia associated with severe sepsis and septic shock results from the counterregulatory hormone and cytokine responses associated with severe illness, coupled with the administration of excess dextrose in intravenous fluids and total parenteral nutrition. Hyperglycemia impairs the phagocytic function of neutrophils and macrophages and results in endothelial dysfunction. The exact protective mechanism of insulin in sepsis is unknown; however, it is believed to be a modulator of numerous inflammatory pathways and an inhibitor of apoptosis. Supplemental insulin has been shown to improve the morbidity and mortality of critically ill patients. In 2001, a randomized controlled trial showed that mechanically ventilated patients treated with an intensive intravenous regimen had a reduction in all-cause mortality from 8.0% to 4.6%. The greatest reduction in mortality was seen in patients who had multiorgan failure and a septic focus. The intensive intravenous insulin regimen also reduced the number of episodes of bacteremia, incidence of acute renal failure requiring hemodialysis, number of transfusions, and incidence of polyneuropathy. A subsequent study showed that an intensive intravenous insulin regimen improved mortality in patients who stayed in the ICU for more than 3 days. In a subgroup of patients who stayed in the ICU less than 3 days, an intensive intravenous insulin regimen increased mortality. In addition, the intensive regimen also had a threefold higher rate of hypoglycemia than the conservative treatment arm. More recently, the Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial, which randomized patients to intensive intravenous insulin or conventional therapy as well as two methods of volume resuscitation, showed similar results after an interim analysis showed higher rates of hypoglycemia (17.0% versus 4.1%), higher rates of serious adverse events, and no difference in mortality. All of these previously mentioned trials with intensive intravenous insulin had a targeted glucose level of 80 to 110 mg/dL. Currently there is a lack of consensus about optimal dosing of intravenous insulin and target glucose levels and current trials are underway to evaluate any differences in clinical outcomes between regimens. Current recommendations for patients who have severe sepsis and hyperglycemia admitted to the ICU are to administer intravenous glucose after initial hemodynamic stabilization with a target glucose level less than 150 mg/dL. Patients on intravenous insulin should have frequent blood
glucose assessments to avoid the adverse consequences of hypoglycemia and consideration should be given to administering a glucose calorie source concurrently with the intravenous insulin.

**BLOOD PRODUCTS ADMINISTRATION**

Anemia is a common problem in severe sepsis and septic shock. Frequent blood sampling for laboratory testing, blood loss from surgical procedures to obtain source control, decreased red blood cell synthesis, and possibly increased red blood cell destruction can contribute to the development of anemia. Decreased red blood cell synthesis may result from the increased septic levels of tumor necrosis factor-α and interleukin-1β that decrease the expression of erythropoietin. Although administration of recombinant human erythropoietin may reduce transfusion requirements, its use does not affect clinical outcomes, such as mortality. If patients have coexisting conditions that warrant its use, consideration can be given to continuing the use of erythropoietin. No target hemoglobin level exists in the setting of severe sepsis and septic shock. During the first 6 hours of septic shock, a target hematocrit of 30% is recommended in patients who have low central venous oxygen saturations. Once tissue hypoperfusion has resolved and there are no extenuating circumstances, such as hemorrhage, myocardial ischemia, or severe hypoxemia, the goal hemoglobin level is subject to debate. In the Transfusion Requirements in Critical Care trial, euolemic critically ill patients were randomized to a restricted target hemoglobin of greater than 7 g/dL or greater than 10 g/dL and were transfused to maintain these targets. Overall mortality was similar between the two groups; however, younger patients who had lower APACHE II scores had overall lower mortality rates with the restricted target when compared with the liberal hemoglobin target. Current recommendations are to maintain a target hemoglobin of 7.0 to 9.0 g/dL and to institute red blood cell transfusions when the hemoglobin decreases to less than 7.0 g/dL. Although no randomized trials exist in severe sepsis and septic shock, recommendations for platelet transfusions are to administer platelets when counts are less than 5000/μL. Higher platelet counts (>50,000/μL) are frequently required for invasive procedures or surgery. Similarly, fresh frozen plasma should be administered in the presence of active bleeding or before surgical or invasive procedures if there is a documented deficiency of coagulation factors as demonstrated by an elevated prothrombin time, partial thromboplastin time, or international normalized ratio.

**MECHANICAL VENTILATION**

Another complication of severe sepsis and septic shock is acute lung injury (ALI) as defined by a partial pressure of oxygen in arterial blood to inspired fraction of oxygen ratio (PaO2/FIO2) of less than 300 mm Hg. Often this lung injury progresses to worsening respiratory failure requiring the initiation of mechanical ventilation. Lung-protective ventilation using relatively low tidal volumes (6 mL/kg predicted body weight) decreases mortality and is beneficial in septic acute lung injury, resulting in lower organ dysfunction and decreased levels of inflammatory cytokines. High tidal volumes and high plateau pressures should be avoided in ALI. The upper limit goal for plateau pressures in a passively inflated patient should be 30 cm H2O or less, with consideration given to chest wall compliance. When appropriate, permissive hypercapnia (elevated partial pressure of carbon dioxide above the baseline) may be allowed to minimize plateau pressures and tidal volumes. Attention should also be given toward maintaining a positive end expiratory pressure (PEEP) level to avoid alveolar collapse and resultant ventilator-induced lung injury. A PEEP level greater
than 5 cm H₂O is usually required to avoid alveolar collapse. Caution should be exercised to avoid overdistension and higher plateau pressures while titrating PEEP. To date, no randomized trials have shown any benefit to one single mode of ventilation when compared to any other mode of ventilation in severe sepsis and septic shock.

**NUTRITION**

Severe sepsis and septic shock are characterized by high energy expenditure, catabolism, and negative nitrogen balance. The use of enteral or parenteral nutrition in severe sepsis and septic shock to correct this problem has been somewhat controversial. Critical illness is associated with gastric dysmotility and bowel ileus, which complicates enteral feeding. In addition, parenteral nutrition has been associated with significant morbidity, such as an increased risk for infection and hepatic dysfunction. Initiation of nutrition is thus often delayed in the critical care setting. More recent studies have suggested that early enteral feeding may reduce morbidity from severe sepsis and septic shock. Early nutrition has been demonstrated to improve wound healing, host immune function, nitrogen balance, and preserve intestinal mucosal integrity. In addition, early enteral nutrition is associated with a lower incidence of infection and shorter hospital length of stay. No improvement in mortality has been documented with initiation of early nutrition, however. In general, the enteral route is preferred over the parenteral route because the parenteral route is more likely to cause hyperglycemia, biliary stasis, and infectious complications. If bowel obstruction, severe acute pancreatitis, major gastrointestinal hemorrhage, or significant hemodynamic instability complicates severe sepsis or septic shock, the enteral route should be avoided. Parenteral nutrition is indicated for patients who have a contraindication to enteral nutrition or when a patient consistently fails enteral feeding trials.

**PROPHYLACTIC MEASURES**

Patients who have severe sepsis or septic shock are at risk for additional complications, such as the development of deep venous thrombosis (DVT), gastrointestinal bleeding, and aspiration of gastric and oral contents. Multiple studies have documented the benefit of DVT prophylaxis in reducing the incidence of venous thromboembolism. All patients who have severe sepsis or septic shock should receive DVT prophylaxis with either low-dose unfractionated heparin or low molecular weight heparin. If a contraindication for anticoagulation exists, patients should receive mechanical prophylaxis with compression stockings or intermittent compression devices. Patients who have severe sepsis or septic shock often require mechanical ventilation, or have a coagulopathy or significant hypotension, all of which are risk factors for gastrointestinal bleeding. Stress ulcer prophylaxis using a proton pump inhibitor or histamine type-2 antagonists should be given to patients who have severe sepsis or septic shock to prevent upper gastrointestinal bleeding. The benefits of acid suppression and prevention of gastrointestinal bleeding should be weighed against the increased stomach pH that results from acid suppression and the incidence of ventilator-associated pneumonia. In addition, the head of the hospital bed should be elevated 30 to 45 degrees in patients who have severe sepsis and septic shock requiring mechanical ventilation to reduce the risk for aspiration and development of ventilator-associated pneumonia. The head of the bed should also be elevated in patients receiving enteral feedings.

Occasionally patients who have severe sepsis or septic shock develop secondary infections throughout the course of the disease. Prior antibiotic use has been associated with the development of fungal infections, which can have significant morbidity and mortality, especially if appropriate antibiotic therapy is delayed. In addition,
the development of cytomegalovirus viremia and *C. difficile* colitis has been reported in patients who have severe sepsis and septic shock. Particular attention should be paid to patients who have prior risk factors (eg, organ transplant recipients and neutropenic patients) for developing secondary infections and opportunistic infections. Consideration can be given to prophylactic use of antibiotics in these high-risk patients, although no recommendations currently exist.

**Biomarkers**

As sepsis progresses to more severe forms of septic shock, global tissue hypoxia emerges with subsequent inflammation, organ dysfunction, and increased mortality. This progression is accompanied by a progression of proinflammatory, anti-inflammatory and apoptotic biomarkers. One failure in the management of sepsis is the difficulty in recognizing the early stages of disease and determining which patients will progress and develop a more severe form of illness. The use of biomarkers has significantly improved the diagnosis and management of other acute diseases, such as coronary artery disease and pulmonary embolism; at present, however, there is no single accepted biomarker or combination of biomarkers for use in patients who have suspected sepsis. Current biomarkers under investigation include pro–brain natriuretic peptide, transcription growth factor β, C-reactive protein, procalcitonin, interleukin-1 receptor antagonist, and intercellular adhesion molecule-1, among others. Procalcitonin and C-reactive protein have been shown to reflect the severity of sepsis and septic shock and can be used to tailor antimicrobial therapies; however, their usefulness in the early phase of sepsis remains questionable. At present the role of biomarkers for diagnosis and prognosis in severe sepsis and septic shock remains undefined.

**Summary**

The diagnosis and management of severe sepsis and septic shock is a complex and dynamic process. Newer evidence-based interventions are constantly being developed and implemented with the purpose of improving morbidity and mortality. Current investigations are being performed in hospital environments to determine the change in behaviors and clinical impact from the most recent Surviving Sepsis recommendations. With the recent updated guidelines, medical institutions frequently follow sepsis protocols incorporating early empiric antibiotics, restoration of tissue perfusion, initiation of vasopressor support, and other supportive measures that have been shown to improve patient outcomes, including overall mortality. A recent study assessing the value of a standardized protocol for patients who have severe sepsis and septic shock demonstrated that those patients who received care adherent to standardized protocols were more likely to receive antimicrobials within 3 hours of presentation, receive appropriate initial antimicrobial treatment, and have a shorten mean length of stay. In another study, patients who had sepsis treated with standardized order sets also have reduced morbidity, such as lower incidence of renal failure and cardiovascular failure and overall improved in-hospital mortality. The use of standardized treatment protocols in addition to newer diagnostic and treatment modalities in patients who have severe sepsis and septic shock can continue to improve patient-related outcomes and the damaging effect of these diseases on society.

**References**


