Sepsis
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Definition
The term systemic inflammatory response syndrome (SIRS) was coined in 1992 by a panel composed of members of the American College of Chest Physicians and Society of Critical Care Medicine. They convened to develop consensus definitions of critical illness for the purposes of clinical trial design. SIRS describes the host response to a critical illness of infectious or noninfectious cause, such as burns, trauma, and pancreatitis. More specific definitions are as follows:

- Sepsis is SIRS resulting from a presumed or known site of infection.
- Severe sepsis is sepsis with an acute associated organ failure.
- Septic shock, a subset of severe sepsis, is defined as a persistently low mean arterial blood pressure despite adequate fluid resuscitation.
- Refractory septic shock is a persistently low mean arterial blood pressure despite vasopressor therapy and adequate fluid resuscitation.

SIRS can be readily diagnosed at the bedside by the presence of at least two of the following four signs: body temperature alterations (hyperthermia or hypothermia), tachycardia, tachypnea, and changes in white blood cell count (leukocytosis or leukopenia).

Prevalence and incidence
Sepsis is the leading cause of death in noncoronary intensive care units (ICUs) and the 10th leading cause of death in the United States overall. The incidence of severe sepsis in the United States is between 650,000 and 750,000 cases. More than 70% of these patients have underlying comorbidities and more than 60% of these cases occur in those aged 65 years and older. When patients with human immunodeficiency virus are excluded, the incidence of sepsis in men and women is similar. A greater number of sepsis cases are caused by infection with gram-positive organisms than gram-negative organisms, and fungal infections now account for 6% of cases.

After adjusting for population size, the annualized incidence of sepsis is increasing by 8%. The incidence of severe sepsis is increasing greatest in older adults and the nonwhite population. The rise in the number of cases is believed to be caused by the increased use of invasive procedures and immunosuppressive drugs, chemotherapy, transplantation, and prosthetic implants and devices, as well as the increasing problem of antimicrobial resistance.

Pathophysiology

Inflammatory Cascade
Severe sepsis can occur as a result of infection at any body site, including the lungs, abdomen, skin or soft tissue, or urinary tract and as a result of a primary bloodstream infection, such as in meningococcemia. Bacteria are the pathogens most commonly associated with the development of sepsis, although fungi, viruses, and parasites can cause sepsis. The pathophysiology of sepsis can be initiated by the outer membrane component of gram-negative organisms (e.g., lipopolysaccharide [LPS], lipid A, endotoxin) or gram-positive organisms (e.g., lipoteichoic acid, peptidoglycan), as well as fungal, viral, and parasitic components (Fig. 1). Signaling by these mediators occurs via a family of transmembrane receptors known as Toll-like receptors. Within the monocyte, nuclear factor-κB (NF-κB), is activated, which leads to the production of proinflammatory cytokines, tumor necrosis factor α (TNF-α), and interleukin 1 (IL-1). TNF-α and IL-1 lead to the production of toxic downstream mediators, including prostaglandins, leukotrienes, platelet-activating factor, and phospholipase A2. These mediators damage the endothelial lining, leading to increased capillary leakage. Furthermore, these
cytokines lead to the production of adhesion molecules on endothelial cells and neutrophils. Neutrophilic endothelial interaction leads to further endothelial injury through the release of the neutrophil components. Finally, activated neutrophils release nitric oxide, a potent vasodilator that leads to septic shock.

**Figure 1: Click to Enlarge**

**Link Between Inflammation and Coagulation**

IL-1 and TNF-α also have direct effects on the endothelial surface. As a result of these inflammatory cytokines, tissue factor, the first step in the extrinsic pathway of coagulation, is expressed on the surfaces of the endothelium and of monocytes. Tissue factor leads to the production of thrombin, which itself is a proinflammatory substance. Thrombin results in fibrin clots in the microvasculature, a sequela most easily recognized in meningococcal septic shock with purpura fulminans. Fibrinolysis is also impained during the septic process. IL-1 and TNF-α lead to the production of plasminogen activator inhibitor-1, a potent inhibitor of fibrinolysis.

Proinflammatory cytokines also disrupt the body’s naturally occurring modulators of coagulation and inflammation, activated protein C (APC) and antithrombin. Protein C circulates as an inactive zymogen but, in the presence of thrombin and the endothelial surface-bound protein thrombomodulin, is converted to the enzyme-activated protein C. Studies have shown that proinflammatory cytokines can shear thrombomodulin from the endothelial surface as well as lead to downregulation of this molecule, thus preventing the activation of protein C. APC and its cofactor protein S turn off thrombin production by cleaving factors Va and VIIIa. APC also restores fibrinolytic potential by inhibiting plasminogen activator inhibitor-1. In vitro studies have revealed that APC has direct anti-inflammatory properties, including inhibiting the production of proinflammatory cytokines by LPS-stimulated monocytes, inhibiting leukocyte adhesion and rolling, and inhibiting neutrophil accumulation.

Antithrombin is the second naturally occurring endothelial regulator affected during sepsis. Antithrombin inhibits thrombin production at multiple steps in the coagulation cascade as well as by binding and inhibiting thrombin directly. Antithrombin, when bound to endothelial cell surface glycosaminoglycans (GAGs), leads to the production of the anti-inflammatory molecule prostacyclin (prostaglandin I$_2$ [PGI$_2$]). Evidence exists that neutrophil elastase cleaves GAGs off the surface of the endothelial lining, thus limiting the anti-inflammatory properties of antithrombin.

**Immunoparalysis**

CD4 lymphocytes play a key role in the inflammatory response seen in sepsis. Early in the sepsis process, these cells assume a TH1 phenotype, where they produce large amounts of the proinflammatory mediators, including interferon gamma, TNF-α, and IL-2. CD4 lymphocytes may evolve over time to a Th2 phenotype, whereby the CD4 lymphocytes produce anti-inflammatory cytokines, including IL-10, IL-4, and IL-13. This is often driven by the release of stress hormones, such as catecholamines and corticosteroids. These cytokines dampen the immune response and can lead to the deactivation of monocytes. Additionally, TNF released early can cause apoptosis of lymphocytes in the gut, leading to further immunosuppression.
Severe Sepsis: The Final Common Pathway
As a result of the vicious cycle of inflammation and coagulation, cardiovascular insufficiency and multiple organ failure occur, and often lead to death. Cardiovascular insufficiency can occur at the level of the myocardium as a result of the myocardial depressant effects of TNF or at the level of the vessel, caused by vasodilation and capillary leak.

Signs and symptoms
Clinical signs that may lead the physician to consider sepsis in the differential diagnosis include fever or hypothermia, unexplained tachycardia, unexplained tachypnea, signs of peripheral vasodilation, unexplained shock, and unexplained mental status changes. Hemodynamic measurements that suggest septic shock are an increased cardiac output, with a low systemic vascular resistance. Abnormalities of the complete blood count (CBC), laboratory test results, clotting factors, and acute-phase reactants might indicate sepsis (Table 1).

Table 1: Laboratory Indicators of Sepsis

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Findings</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>White blood cell count</td>
<td>Leukocytosis or leukopenia</td>
<td>Endotoxemia may cause early leukopenia</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Thrombocytosis or thrombocytopenia</td>
<td>High value early may be seen as acute-phase response; low platelet counts seen in overt DIC</td>
</tr>
<tr>
<td>Coagulation cascade</td>
<td>Protein C deficiency; antithrombin deficiency; elevated D-dimer level; prolonged PT and PTT</td>
<td>Abnormalities can be observed before onset of organ failure and without frank bleeding.</td>
</tr>
<tr>
<td>Creatinine level</td>
<td>Elevated from baseline</td>
<td>Doubling-indicates acute renal injury</td>
</tr>
<tr>
<td>Lactic acid level</td>
<td>Lactic acid &gt; 4 mmol/L (36 mg/dL)</td>
<td>Indicates tissue hypoxia</td>
</tr>
<tr>
<td>Liver enzyme levels</td>
<td>Elevated alkaline phosphatase, AST, ALT, bilirubin levels</td>
<td>Indicates acute hepatocellular injury caused by hypoperfusion</td>
</tr>
<tr>
<td>Serum phosphate level</td>
<td>Hypophosphatemia</td>
<td>Inversely correlated with proinflammatory cytokine levels</td>
</tr>
<tr>
<td>C-reactive protein (CRP) level</td>
<td>Elevated</td>
<td>Acute-phase response</td>
</tr>
<tr>
<td>Procalcitonin level</td>
<td>Elevated</td>
<td>Differentiates infectious SIRS from noninfectious SIRS</td>
</tr>
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ALT, alanine aminotransferase; AST, aspartate transaminase; DIC, disseminated intravascular coagulation; PT, prothrombin time; PTT, partial thromboplastin time; SIRS, systemic inflammatory response syndrome.

Conditions other than sepsis can produce a systemic inflammatory response and organ dysfunction. Noninfectious illnesses that should be considered in the differential diagnosis include tissue injury caused by trauma, hematoma, venous thrombosis, myocardial or pulmonary infarcts, transplant...
rejection, pancreatitis, hyperthyroidism, addisonian crisis, drug or blood product reaction, malignancies, and central nervous system hemorrhages.17

Diagnosis
The diagnosis of severe sepsis requires the presence of a presumed or known site of infection, evidence of a systemic inflammatory response, and an acute sepsis-associated organ dysfunction. Following is a description of the specific diagnostic criteria used in past clinical trials to define patients with severe sepsis.

- A presumed or known site of infection is indicated by one of the following:
  - Purulent sputum or respiratory sample, or chest radiograph with new infiltrates not explained by a noninfectious process
  - Spillage of bowel contents noted during an operation
  - Radiographic or physical examination evidence of an infected collection
  - White blood cells in a normally sterile body fluid
  - Positive blood culture
  - Evidence of infected mechanical hardware by physical or radiographic examination

- Evidence of a systemic inflammatory response is indicated by at least two of the following:
  - Fever or hypothermia: core body temperature 38° C or higher or 36° C or lower
  - Tachypnea: 20 breaths/min or more, or need for mechanical ventilation for an acute process
  - Tachycardia: heart rate 90 beats/min or more, unless the patient has a preexisting tachycardia
  - White blood cell count:12,000 cells/mm³ or higher, 4,000 cells/mm³ or less, or more than 10% bands on differential

- A sepsis-induced organ failure is indicated by one of the following criteria:
  - Cardiovascular dysfunction: mean arterial pressure 60 mm Hg or lower, the need for vasopressors to maintain this blood pressure in the presence of adequate intravascular volume (central venous pressure >8 mm Hg or pulmonary artery occlusion pressure >12 mm Hg), or after an adequate fluid challenge has been given
  - Respiratory organ failure: an arterial oxygen pressure-to-fraction of inspired oxygen ratio of less than 250 in the absence of pneumonia or less than 200 in the presence of pneumonia
  - Renal dysfunction: urine output less than 0.5 mL/kg/hr for 2 hours in the presence of adequate intravascular volume or after an adequate fluid challenge or doubling of the serum creatinine level
  - Hematologic dysfunction: thrombocytopenia with less than 80,000 platelets/mm³, or 50% decrease from baseline during the acute illness
  - Unexplained metabolic acidosis: pH lower than 7.30 and plasma lactate level higher than 1.5 times the upper limit of normal for the laboratory

Summary
- The diagnosis of severe sepsis includes the presence of a systemic inflammatory response and an end-organ failure in the setting of infection.
- The inflammatory and coagulopathic responses to infection cause the end-organ failure seen in sepsis.
- Noninfectious causes should be considered in the differential diagnosis of SIRS.
- The physical examination and radiographic tests should focus on three major sites of sepsis: lungs, abdomen, and urinary tract.
- Elevated lactic acid levels and coagulation abnormalities are early laboratory indicators of sepsis.

Treatment

Practice Guidelines

Eleven societies involved in the care of the critically ill collaborated to produce guidelines for the care of patients with severe sepsis, published in 2004. However, the individual treatment guidelines have not been universally agreed on. Additionally, new clinical trial data have been reported since these guidelines were initially published.

Appropriate Antimicrobial Treatment

Many clinical studies have demonstrated a twofold increase in mortality caused by sepsis when inappropriate antimicrobial therapy is given. More recent animal and human studies have demonstrated an incremental but statistically significant increase in mortality with each hour delay in the administration of appropriate antibiotic therapy from the onset of septic shock. When the clinician encounters a patient with severe sepsis, the site of infection and causative organism(s) often are unknown. Empirical antibiotics must be given in these cases. Appropriate empirical antimicrobial therapy must be guided by the knowledge of the most common sites of infection and the most common infecting organisms. A clinical trial of patients with severe sepsis has revealed that the lungs are the most common sites of infection, followed by the abdomen and urinary tract. In terms of pathogen type, gram-positive organisms cause sepsis slightly more often than gram-negative organisms; fungal organisms account for approximately 6% of cases. The most common gram-positive organisms are *Staphylococcus aureus* and *Streptococcus pneumoniae*, and the most common gram-negative organisms are *Escherichia coli*, *Klebsiella* spp., *Pseudomonas* spp., and *Enterobacter* spp. Samples for blood cultures should be taken from a percutaneous site and from any intravascular catheters. Samples for Gram staining and culture should be taken from suspected sites of infection. Table 2 indicates appropriate empirical antibiotic choices by site of infection.

**Table 2: Empirical Antimicrobial Therapy for Major Sites of Sepsis**

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Microorganisms</th>
<th>Therapeutic Choices</th>
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<tbody>
<tr>
<td>Community-acquired pneumonia</td>
<td><em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, <em>Legionella pneumophila</em>, <em>Mycoplasma pneumoniae</em></td>
<td>Third-generation cephalosporin with macrolide or respiratory quinolone</td>
</tr>
<tr>
<td>Early hospital-acquired pneumonia (&lt;5 days)</td>
<td><em>S. pneumoniae</em>, <em>H. influenzae</em>, <em>L. pneumophila</em>, <em>M. pneumonia</em>; nonresistant gram-negative rods</td>
<td>Ceftriaxone, respiratory quinolone or ampicillin-sulbactam, or ertapenem</td>
</tr>
<tr>
<td>Late hospital-acquired pneumonia</td>
<td><em>Pseudomonas aeruginosa</em>, <em>Klebsiella</em> spp., <em>Acinetobacterspp.</em>, methicillin-resistant <em>Staphylococcus aureus</em></td>
<td>Antipseudomonal cephalosporin or carbapenem, or antipseudomonal beta-lactam or beta-lactamase inhibitor, <em>plus</em> linezolid or vancomycin</td>
</tr>
<tr>
<td>Intra-abdominal infections</td>
<td>Enteric gram-negative rods and anaerobes</td>
<td>Third-generation cephalosporin with metronidazole, or beta-lactam or beta-lactamase inhibitor, or carbapenem or moxifloxacin</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Gram-negative rods; <em>Enterococcus</em> spp.</td>
<td>Extended-spectrum beta-lactam or aztreonam, with or without an aminoglycoside; ampicillin or vancomycin if <em>Enterococcus</em> is present</td>
</tr>
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Empirical antifungal therapy should be given to patients at high risk for fungemia. High-risk patients include those who have had prior colonization with *Candida* at two or more sites, those being treated with more than two different antibiotics, those who have taken antibiotics for more than 14 days, those who have had prior placement of a Hickman catheter, and those who have undergone prior hemodialysis. 21

**Source Control of Infection**

Adequate source control of infection is as important as appropriate antimicrobial therapy in the treatment of a patient with severe sepsis. Source control of infection includes removal of infected foreign bodies, such as urinary catheters, intravascular catheters, peritoneal dialysis cannulas, prosthetic joints, vascular grafts, and mechanical valves. Incision and drainage of cutaneous abscesses as well as open or percutaneous drainage of intra-abdominal abscesses also fall under the principle of adequate source control of infection. 22 Furthermore, one specific clinical scenario requires specific mention. For patients with necrotizing fasciitis, mortality and extent of tissue loss are directly related to the rapidity of surgical intervention.

**Optimizing Tissue Oxygenation**

Optimizing the delivery of oxygen to critical organs is an urgent priority in the treatment of severe sepsis. The inability to meet tissue oxygen demand can be determined at the time of a patient's presentation to the emergency department by the presence of lactic acidosis (serum lactic acid level >4 mmol/L or 36 mg/dL). In this setting, the use of early goal-directed therapy (EGDT) to achieve a central venous oxygen saturation of 70% or higher has been shown to reduce mortality as well as hospital resources. EGDT is accomplished by first placing a central venous catheter to monitor the central venous oxygen saturation. Crystalloid boluses of 500 mL are given every 30 minutes to reach a central venous pressure (CVP) of 8 to 12 mm Hg. If the mean arterial pressure (MAP) is still below 65 mm Hg, vasopressor agents are added. If after these maneuvers the central venous oxygen saturation remains below 70%, red blood cells are transfused to reach a hematocrit of 30%. If the target is still not reached, dobutamine is then administered. 23

**Fluid Resuscitation**

The best type of fluid replacement and optimal volume of resuscitation in the setting of severe sepsis have been heavily debated but studies have provided guidance to the clinician. One trial comparing 4% albumin with normal saline for fluid resuscitation found no difference in mortality at 28 days. 24 A 2004 meta-analysis similarly found no mortality advantage with the use of colloids compared with the use of crystalloids. 25 The trial of EGDT revealed that patients in the treatment arm received far greater volumes of fluid in the first 6 hours of resuscitation than those in the control arm. In a large study of European ICUs, patients with a positive fluid balance at 72 hours had a poor outcome. 26 In a clinical trial of patients with acute lung injury, the use of a conservative fluid strategy targeting a CVP lower than 4 mm Hg and a pulmonary artery occlusion pressure (PAOP) lower than 8 mm Hg was associated with a fewer number of ICU and ventilators days. 27 The preponderance of data would suggest that aggressive fluid management be done in the acute phase of sepsis, followed by a more conservative phase in the following few days.

**Vasopressor Treatment**

Dopamine and norepinephrine are the first-line agents for the treatment of sepsis shock. Dopamine increases cardiac index and systemic vascular resistance, whereas norepinephrine is a potent
vasoconstrictor with few cardiac effects. A clinical trial comparing dopamine and norepinephrine in fluid-resuscitated patients with septic shock demonstrated a greater reversal of hypotension and lower mortality with the use of norepinephrine. Norepinephrine also has the added advantage of causing fewer tachyarrhythmias than dopamine and does not suppress the hypothalamic-pituitary axis. Second-line agents for the treatment of septic shock include epinephrine, phenylephrine, and vasopressin. The use of epinephrine and phenylephrine is hampered by both drugs’ negative effects on splanchnic blood flow. Vasopressin has become the agent of choice in cases of septic shock refractory to dopamine, norepinephrine, or both. Studies have demonstrated that vasopressin increases blood pressure and allows dopamine and norepinephrine drips to be weaned.

**Low-Dose Corticosteroid Treatment for Septic Shock**

Corticosteroids have long been considered to be of potential use in the treatment of severe sepsis because of their anti-inflammatory properties and beneficial effects on vascular tone. Clinical trials of high-dose, short-course corticosteroids have not demonstrated benefits in mortality in patients with severe sepsis; however, trials of long-course, low-dose corticosteroids (<200 mg/day of hydrocortisone for ≥5 days) have demonstrated a shorter time to shock reversal and improved mortality compared with placebo. The largest of these trials, performed by Annane and colleagues, has shown an improved survival time with the use of hydrocortisone, 50 mg every 6 hours, and with fludrocortisone, 50 µg/day for 5 days, in patients with refractory septic shock no longer than 8 hours in duration who did not respond with a 9-µg/dL rise in the cortisol level 1 hour following adrenocorticotropic hormone (ACTH) stimulation. This trial has suggested a treatment benefit with corticosteroids only in patients with adrenal insufficiency or adrenal resistance caused by sepsis. A meta-analysis, however, did not reveal that treatment benefit is related to ACTH test results. A study by Hamrahian and colleagues of free cortisol levels in this population revealed a low incidence of adrenal insufficiency. A larger trial (CORTICUS) in a less severely ill population with septic shock than the Annane trial did not reveal a mortality benefit with low-dose, long-course corticosteroids but suggested a shorter time to shock reversal. A higher incidence of hyperglycemia and superinfections was observed in the corticosteroid-treated arm. Current clinical evidence would suggest treating only patients with shock refractory to vasopressors with low-dose, long-course corticosteroid therapy. Results of an ACTH test are not necessary to determine which patients should be treated.

**Recombinant Human Activated Protein C**

Activated protein C is a molecule with anti-inflammatory, antithrombotic, and profibrinolytic properties. In a large placebo-controlled, randomized, clinical trial in patients with severe sepsis, recombinant human activated protein C (rhAPC), 24 µg/kg/hour for 96 hours, was associated with a 6% absolute reduction in 28-day all-cause mortality compared with placebo. The treatment benefit was confined to patients with greatest disease severity, as indicated by a baseline APACHE II score higher than 25 or those with two or more organ failures at baseline. Retrospective analyses would suggest that patients with severe sepsis caused by community-acquired pneumonia and those with overt DIC may be the most ideal target populations for this agent.

The main adverse event associated with rhAPC is bleeding. Bleeding tends to occur in patients with severe thrombocytopenia and in those with a known disruption of blood vessels or ulcerative gastrointestinal lesions. RhAPC is not approved for children or surgical patients with sepsis and a single organ failure. Children with purpura fulminans, a profound state of protein C deficiency caused by infection with Neisseria meningitidis or Streptococcus pneumoniae, should be considered for treatment with rhAPC given the high mortality rate and amputation rates associated with this syndrome.

**Glycemic Control**

Tight control of the blood glucose level during sepsis might be expected to decrease the rate of infectious complications and improve outcomes in patients with sepsis. In a clinical trial conducted in a surgical ICU predominantly in patients following cardiac surgery, maintaining the blood glucose level
below 110 mg/dL was associated with improved survival, fewer blood stream infections, shorter ICU stays, and fewer episodes of acute renal failure compared with a group in whom the glucose level was maintained between 180 and 200 mg/dL. A second study completed in the medical ICU showed a mortality benefit with tighter glycemic control only in patients with stays in the ICU of 3 days or longer. A threshold glucose level of 145 mg/dL was associated with improved mortality in a prospective observational study. A German trial (VISEP) was stopped when mortality was not improved in the tight glycemic control arm and more hypoglycemic events were observed. Current data suggest targeting a blood glucose level of no lower than 150 mg/dL in a critically ill patient.

**Ventilator Treatment for Acute Respiratory Distress**

Thanks to the efforts of organized networks of acute respiratory distress syndrome (ARDS) investigators in the United States and elsewhere, much has been learned about the appropriate ventilator management of patients with ARDS caused by sepsis. A randomized clinical trial has demonstrated lower mortality and an increase in the number of days off the ventilator when a lower (6 mL/kg) tidal volume strategy is used compared with a standard (12 mL/kg) tidal volume strategy. A second study using the lower tidal volume strategy examined the optimal amount of PEEP (positive end-expiratory pressure) that should be administered to patients with ARDS. This study found that low levels of PEEP (<14 cm H₂O) produced similar outcomes as high PEEP (>14 cm H₂O). A clinical trial of nitric oxide indicated that this agent is capable of transient improvements in oxygenation without an improvement in mortality or number of ventilator days. Similar findings were observed with prone position ventilation. However, neither nitric oxide use nor prone position ventilation can be recommended routinely for all patients with sepsis and ARDS based on randomized studies.

**Blood Transfusions**

Blood transfusions in the critically ill have the potential to increase oxygen-carrying capacity but also entail an increased risk of nosocomial infection. In the EGDT protocol, transfusing red blood cells to achieve a hematocrit of 30% was used as part of the strategy to reach a central venous oxygen saturation of 70% during the first 6 hours of hospital stay. A study by Hebert and colleagues in critically ill patients demonstrated that maintaining hemoglobin between 7 and 9 mg/dL and transfusing only when the hemoglobin drops below 7 mg/dL is not associated with a worse outcome than maintaining the hemoglobin above 10 g/dL. The data would suggest early use of transfusions in the acute setting of sepsis, followed by a conservative strategy once tissue oxygen demands have been reached.

**Additional Treatment Components**

Three additional components in the care of severe sepsis patients include ensuring adequate nutrition, providing deep venous thrombosis prophylaxis, and providing gastric ulcer prophylaxis. Adequate nutrition is best accomplished enterically to avoid catheter-related blood stream infections, maintain gut mucosa integrity, and prevent the theoretical possibility of translocation of bacteria across the intestinal wall. A mortality benefit with enteral feeds containing omega-3 fatty acids compared with standard enteral feeds was observed in a small clinical trial of patients with severe sepsis. A morbidity benefit was observed with this same formula in patients with ARDS. Deep venous thrombosis prevention can be accomplished with the use of subcutaneous heparin or continuous use of pneumatic compression stockings. Gastric ulcer prophylaxis may be accomplished with sucralfate, an H2 receptor antagonist, or a proton pump inhibitor.

**Summary**

- Antibiotic therapy should be administered within 1 hour of the acute presentation of sepsis.
- Patients with lactic acidosis should be placed on an early goal-directed therapy protocol.
- A low tidal volume ventilator strategy and a conservative fluid strategy should be used in patients with established acute lung injury.
Recombinant human activated protein C use should be considered in the setting of an APACHE II score higher than 25 or the presence of two or more organ failures.

Low-dose corticosteroid therapy should be considered for patients with septic shock refractory to fluid resuscitation and vasopressors (MAP <60 mm Hg).

Outcomes
Although the incidence of severe sepsis is increasing, mortality rates continue to decrease. In a recent study in a sepsis cohort, the mortality rate was 24.4%. Age was found to be an independent risk factor for death with a mortality rate of 27.7% in those older than 65 years versus 17.7% in those younger than 65 years of age. An increasing number of older survivors of sepsis require skilled nursing facilities following discharge from the hospital.

Prevention
Because pneumonia is the most common infection leading to sepsis, efforts to decrease the incidence of this infection would lead to the most rapid reduction in new sepsis cases. Every effort should be made to vaccinate susceptible individuals against influenza, H. influenzae, and S. pneumoniae. Additionally, asplenic patients should receive vaccination against N. meningitidis as should college students living in dormitories. The incidence of intravascular catheter-related bloodstream infections can be diminished by strict procedures to ensure sterile insertion, as well as the use of chlorhexidine dressings at the exit site. Cases of ventilator-associated pneumonia can be decreased by maintaining ventilator patients semirecumbent at a 45-degree angle.

Suggested Readings

References


