Severe sepsis is one of the most significant concerns in the treatment of critical care patients, with more than 750,000 cases occurring annually. The condition spreads quickly, is often difficult to recognize, and has a mortality rate of 28% to 50%. Identification of patients at high risk for progressing to severe sepsis is critical, and in many cases, monitoring patients rather than evaluating for treatment, can increase the risk of mortality.

The financial implications of severe sepsis are substantial. Severe sepsis costs an average of $22,000 per patient, with a total cost to US hospitals of $16.7 billion. The cost of treating a patient in the ICU with severe sepsis is 6 times greater than the cost of treating a patient in the ICU who does not have sepsis.

The role of nurses in preventing the spread of severe sepsis is crucial, because they are in the position to identify patients at the first sign of becoming septic. Recognizing the signs that a patient has sepsis or has risk factors for developing sepsis allows appropriate treatment to begin early in the course of the condition. The sooner that treatment of sepsis begins, the less likely that it will spread to involve the patient's organs and start a life-threatening cascade of events.

In October 2002, Phase I of the Surviving Sepsis Campaign was initiated to increase education regarding this condition and to establish guidelines to dictate appropriate early treatment of patients at risk for progressing to severe sepsis. In progressing to Phase II, 11 international healthcare associations gathered in 2003 to develop a consensus opinion on steps that should be taken in the ICU when treating patients with severe sepsis in order to reduce overall mortality.

Although these guidelines offer hope of reducing mortality caused by sepsis, the optimal course of action is prevention. Hand disinfection, early removal of invasive tubes and catheters, 30° head elevation for patients on mechanical ventilation, early enteral nutrition, and adherence to the CDC Guidelines for avoiding antibiotic resistance can limit the opportunity for infections that can lead to sepsis.

PATHOPHYSIOLOGY OF SEPSIS
Recognizing the risk of developing severe sepsis requires an understanding of the body's systemic response to infection (Figure 1). During a normal response, when an antigen enters the bloodstream, the immune system releases proinflammatory mediators, including TNF-α (tumor necrosis factor), IL-1β (interleukin), chemokines, prostaglandins, and platelet-activating factor, to clear the antigen and promote recovery of affected tissue. The coagulation cascade is initiated, converting fibrinogen to fibrin, leading to the development of a clot to isolate the antigen. To maintain this clot, plasminogen activator inhibitor-1 and thrombin activatable fibrinolysis inhibitor are released to suppress fibrinolysis, which is necessary to allow the time needed to destroy the antigen before the body lyses the clot.

With the antigen isolated, the proinflammatory mediators attract activated neutrophils, which engulf the antigen. To prevent the proinflammatory response from damaging normal tissues, anti-inflammatory mediators are released, including IL-4 and TGF-β (transforming growth factor). The balance of inflammatory and anti-inflammatory mediators restricts the inflammatory response to the local site of the infection.

This article has been designated for CE credit. A closed-book, multiple-choice examination follows this article, which tests your knowledge of the following objectives:

1. Identify the signs of systemic inflammation
2. Distinguish among the sepsis identification definitions
3. Discuss the components of the new Surviving Sepsis Campaign guidelines
4. Describe essential aspects of treatment for severe sepsis

FACULTY DISCLOSURES
Deborah Tuggle, RN, MN, CCNS, is on the lecture bureau for Eli Lilly and Company.
Tom Ahrens, RN, DNS, CCRN, CS, is on the lecture bureau for Eli Lilly and Company and receives research funds from KCI and Abbott.
When sepsis occurs, this balance is upset and the immune response is not localized to the area around the antigen, but becomes systemic. The excess coagulation, exaggerated inflammation, and impaired fibrinolysis associated with the immune response quickly spread beyond the infected area. The imbalance of the immune response favors coagulation, with increased generation of thrombin and deposition of fibrin. These fibrin clots lead to microvascular hypoperfusion, diminished oxygen delivery, and tissue necrosis. Organ failure follows and the condition progresses to severe sepsis. The procoagulant state results in further endothelial damage, while the vascular damage caused by coagulation leads to the release of more neutrophils and inflammatory cytokines.

This self-perpetuating chain of events results in decreased blood flow to organ tissue. Cardiac output may remain normal or even increase but, at the capillary level, tissue perfusion is impeded and oxygenation is impaired. Tissue oxygenation is a critical indicator of sepsis that can be detected before organ failure occurs. An effective means of assessing tissue oxygenation is to measure the oxygen saturation of central venous or mixed venous blood (SVo2), which reflects the amount of oxygen left in the blood after completing circulation. Normal SVo2 saturation is approximately 60% to 75%, with the remaining 25% to 40% having been extracted during circulation.12

Generally in severe sepsis, clotting will obstruct microcapillary perfusion, causing increases in SVo2 levels. In some cases, blood flow is decreased, and the tissue will extract a higher percentage of available oxygen, reducing SVo2 levels. Therefore, in severe sepsis, any variation from normal SVo2 levels should be viewed as consistent with severe sepsis.

The causes of sepsis are not fully understood, making treatment difficult. Factors associated with increased risk of developing sepsis include trauma to the gastrointestinal tract, perforation of the small intestine, surgery, chronic debilitating conditions such as diabetes, use of invasive procedures and devices in the ICU setting, and treatment with immunosuppressant drugs.13

PATIENT IDENTIFICATION

Early identification of severe sepsis is crucial, as the patient’s risk of mortality increases rapidly if the condition spreads to involve multiple organs (Figure 2).1,14 Sepsis-associated mortality following the failure of 1 organ is approximately 20%. When 2 organs fail, the rate of mortality is approximately 40%. The mortality rate when 3 organs fail is 65% to 70% and 75% to 85% when 4 or more organs fail.

Currently, recognizing patients at risk for developing sepsis is difficult due to limited identifying signs and symptoms. However, researchers are assessing biomarkers that will indicate patients at risk, similar to using troponin to identify patients at risk for a myocardial infarction. Protein C levels have been identified as a potential indicator for the development of sepsis.15

Until these biomarkers have been established, physical guidelines are used to identify patients at risk.
Keys to identifying a patient with severe sepsis:
1. The patient must have an infection or suspected infection.
2. The patient must have 2 or more systemic inflammatory response syndrome (SIRS) criteria, as established by 1991 American College of Chest Physicians/Society of Critical Care Medicine guidelines (Table 1). Any patient who has a known or suspected infection and shows these signs of inflammation should be treated as a likely sepsis candidate.
3. When a patient with sepsis fails to respond to fluid resuscitation and suffers perfusion abnormalities, the patient has developed septic shock, during which chemical mediators are released which may cause more cell damage.
4. Severe sepsis occurs when sepsis is combined with dysfunction of at least 1 organ. However, the connection between 1 organ failing and the possibility that the patient has severe sepsis is often overlooked. All patients with infections should be closely monitored for the development of severe sepsis, but nurses must also recognize other subtle, crucial indicators. For example, if a patient who is being treated for pneumonia experiences a worsening clinical picture or another organ involvement, such as a significant decrease in urine output or requires mechanical ventilation, the nurse should recognize that these are indicators of a deteriorating situation and that severe sepsis may be present. One of the most dangerous signs is when a patient who is receiving antibiotics requires a vasopressor. Due to the high risk of death associated with the need for vasopressors, the combination of antibiotics and vasopressors should be an immediate signal for evaluation of the patient for severe sepsis.

Other important indications of organ dysfunction include altered consciousness, tachypnea, tachycardia, urine output of less than 0.5 mL/kg/hour, platelet count less than 80 000/mm$^3$ or a 50% decrease in platelets over 3 days, and unexplained metabolic acidosis (Figure 3).

**TREATMENTS**

The goals of sepsis treatment are to manage the infection and the body’s response to the infection. Preventing sepsis is always the best option. However, once an infection is present, treatment must be prompt. Empiric antibiotic therapy should be instituted to control the original source of the infection (with blood cultures guiding treatment whenever possible). However, once severe sepsis has begun, treatment options are limited. In order to standardize treatment options, the Surviving Sepsis Campaign provided several evidence-based treatments for severe sepsis. The goal of providing these guidelines is to standardize the treatment of severe sepsis and generate an improved outcome.

**SURVIVING SEPSIS CAMPAIGN**

The Surviving Sepsis Campaign is a worldwide project with the goal of decreasing mortality due to sepsis by 25% in the next 5 years. It reflects the commitment and deliberation of critical care experts from 11 international organizations. After more than a year of systematic review and study, 45 recommendations for care were announced and officially implemented in

---

**Table 1 Clinical definitions**

**Sepsis:** Known or suspected infection plus 2 or more of the following SIRS criteria:

**SIRS Criteria:**
- Core temperature >38°C or <36°C
- Tachycardia (>90 beats/minute)
- Tachypnea (>20 breaths/minute, PaCO$_2$ <32 mm Hg, or mechanical ventilation)
- White blood cell count >12,000/mm$^3$ or <4000/mm$^3$ or >10% mature neutrophils

**Severe Sepsis:** Sepsis plus dysfunction of at least 1 organ

**Septic Shock:** Sepsis plus
- Hypotension despite fluid resuscitation and perfusion abnormalities

---

Copyright © 2003, Eli Lilly and Company. All rights reserved. Printed with permission.
Many of the Surviving Sepsis Campaign’s suggestions relate to reasonable and prudent care of any critically ill patient, not just those with sepsis. For example, there is guidance for prophylaxis of venous thromboembolism and stress ulcers, along with directives related to the use of sedatives, paralytics, and renal replacement therapy. The Surviving Sepsis Campaign evaluated the available scientific data regarding severe sepsis from level I, large randomized trials, to level V, case studies, uncontrolled studies, and expert opinion (Table 2). The campaign used these designations to rank the currently available treatments for sepsis based on the quality of the science supporting their use. Grade A treatments have the best evidence to support their use, whereas grade E modalities are based on weaker levels of evidence (Table 3).

In terms of treating severe sepsis, currently there is no grade A treatment. However, there are 2 grade B treatments:

1. Recombinant Human Activated Protein C [rhAPC or Xigris (drotrecogin alfa [activated], Eli Lilly and Co, Indianapolis, Ind)]

2. The early goal-directed therapy program.

There were 2 grade C treatments, i.e., replacement dose steroid therapy and fluid therapy. There is 1 grade D treatment, i.e., tight glucose regulation and 2 grade E treatments, i.e., vasopressors and inotropes.

Although a few grade A-designated sanctions are included in the guidelines, most of the suggestions relate to avoiding what has been proven not to work in sepsis or general critical care strategies, such as ventilator weaning. More than half the 45 recommendations in the Campaign are based on nonrandomized studies, case studies, or expert opinion, reflecting our limited knowledge in managing the septic patient.

Making the public aware of the Surviving Sepsis Campaign guidelines will contribute to the goal of decreasing mortality by helping people recognize warning signs of sepsis. Similar efforts have been successful in educating individuals regarding the signs of a heart attack or a “brain attack.” If the public can be taught about early recognition of a “sepsis attack,” they may be able to seek and receive care before it is too late.

A review of the suggested treatments will help clarify the Surviving Sepsis Campaign guidelines.

**Goal-Directed Therapy** – Because the unchecked coagulation cascade leads to tissue hypoxia, one treatment that has been attempted is early goal-directed therapy to optimize cardiac output. Infusions of colloid or crystalloid, vasoactive agents, and transfusions of red blood cells are used to increase oxygen delivery, with the goal of normalizing SVO2, lactate concentration, base deficit, and pH. In one trial, patients on early goal-directed therapy received more fluid, inotropic support, and blood transfusions during the first 6 hours than the control group, who received standard fluid therapy. During the first 72 hours of treatment, patients receiving the goal-directed therapy had a higher central venous oxygen concentration, lower lactate concentration, lower base deficit, and higher pH than the control group. Mortality was also lower in the aggressive treatment group (30.5%) than in the control group (46.5%).

**Recombinant Human Activated Protein C (rhAPC)** – rhAPC is the human recombinant form of endogenous activated protein C, a naturally occurring protein that modulates the coagulation cascade. Endogenous activated protein C may inhibit plasminogen activator inhibitor (PAI-1), which prevents tissue-type plasminogen activator (t-PA) from binding to fibrin. By facilitating t-PA activity, activated protein C promotes fibrinolysis. Activated protein C inhibits the development of clots that form unnecessarily and reduces the effect of the body’s inflammatory mediators, including neutrophils. Based on its ability to inhibit cytokine release by activated monocytes, activated protein C also may have anti-inflammatory properties (Figure 4).

In severe sepsis, protein C levels are significantly depleted. Administration of rhAPC restores balance to the systemic irregularities that occur during sepsis and allows a return to homeostasis in the microvasculature. In the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, Xigris reduced the rate of mortality in patients with severe sepsis by 6%, while reducing the mortality rate for those at high risk of death by 13%.

Food and Drug Administration (FDA) guidelines for Xigris indicate use for patients at high risk for death, such as patients having an Acute Physiology and Chronic Health

---

**Table 2** Levels of scientific evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Large, randomized trials with definitive results; low risk of false-positive or false-negative error</td>
</tr>
<tr>
<td>Level II</td>
<td>Small, randomized trials with uncertain results; moderate-to-high risk of false-positive or false-negative error</td>
</tr>
<tr>
<td>Level III</td>
<td>Nonrandomized, contemporaneous controls</td>
</tr>
<tr>
<td>Level IV</td>
<td>Nonrandomized, historical controls, and expert opinion</td>
</tr>
<tr>
<td>Level V</td>
<td>Case studies, uncontrolled studies, and expert opinion</td>
</tr>
</tbody>
</table>

**Table 3** Grades of treatment recommendations

<table>
<thead>
<tr>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>Supported by at least 2 level I investigations</td>
</tr>
<tr>
<td>Grade B</td>
<td>Supported by 1 level I investigation</td>
</tr>
<tr>
<td>Grade C</td>
<td>Supported by level II investigations only</td>
</tr>
<tr>
<td>Grade D</td>
<td>Supported by at least 1 level III investigation</td>
</tr>
<tr>
<td>Grade E</td>
<td>Supported by level IV or V evidence</td>
</tr>
</tbody>
</table>
Evaluation (APACHE) II score of 25 or greater (25% chance of mortality), current use of vasopressors (32% chance of mortality), or failure or dysfunction of 2 organs (greater than 40% chance of mortality). In addition, the Extended Evaluation of Recombinant Human Activated Protein C (ENHANCE) trial showed early use of Xigris considerably shortened time in the ICU for patients with severe sepsis.22

However, many hospitals have been slow to utilize Xigris as an early treatment. Two primary issues are related to the slow use of Xigris: the potential risk of bleeding and cost of the drug.

Overall, the risk of death from bleeding among patients receiving Xigris was low, i.e., 0.5% in the PROWESS trial.23 Serious bleeding events occurred in 3.5% of patients who received Xigris and 2.0% of patients receiving placebo. The majority of patients who experienced bleeding were predisposed to bleeding as a result of conditions including trauma, gastrointestinal tract ulceration or severe coagulopathies. The rate of intracranial hemorrhage was 0.2% in patients receiving Xigris and 0.1% in patients receiving placebo. Among the 850 patients who received Xigris, there were 4 deaths, compared to 2 deaths in the placebo arm. No thrombotic strokes occurred among patients who received Xigris compared to 5 in the patients who received placebo. The potential bleeding risk of Xigris (rhAPC) is low compared to the risk of death from sepsis.

The FDA contraindications are for patients who are actively bleeding or have a condition that carries a high risk of death from bleeding, such as recent hemorrhagic stroke or head trauma. In cases where there is concern of bleeding or if the patient must undergo surgery, Xigris can be stopped and, within 30 minutes, 80% of the medication will pass out of the system. Within 2 hours, the drug is completely cleared.

In terms of cost, a 96-hour infusion of Xigris in a 70-kg patient costs approximately $6800. Recently published studies suggest that this cost is offset by the cost savings in removing patients from the ICU more rapidly.22,24

The ENHANCE trial examined 2378 patients who received Xigris. Patients who received Xigris in the first 24 hours of diagnosis of severe sepsis had a mortality rate of 33%, compared to a mortality rate of 41% in patients who were treated after 24 hours (Figure 5).22 Patients who received Xigris in the first 24 hours spent 4 fewer days in the ICU and spent 3 fewer days on mechanical ventilation

![The Role of Endogenous Activated Protein C in Patients with Severe Sepsis](image)

**Figure 4** Protein C levels are depleted in patients in severe sepsis. Administration of activated protein C helps restore homeostasis.

Copyright © 2002, Eli Lilly and Company. All rights reserved. Printed with permission.

![Mortality for Patients in PROWESS and ENHANCE](image)

**Figure 5** The ENHANCE trial showed that early administration of activated drotrecogin alfa significantly reduced mortality.22

Copyright © 2002, Eli Lilly and Company. All rights reserved. Printed with permission.

![Mortality for Patients in PROWESS and ENHANCE](image)
Daily costs associated with ICU stays range between $1000 and $3000, so a 4-day stay in the ICU costs between $4000 and $12,000. Cost may be a greater concern if treatment is started later in the course of severe sepsis, but early treatment with Xigris may offset the overall cost.

Fluid Therapy – Fluid therapy is most effective early in the course of severe sepsis because, as the condition worsens, there is greater dysfunction at the cellular level. Excess coagulation and impaired fibrinolysis lead to disruption of the endothelial wall, which makes capillaries more permeable. Once severe sepsis is present, the potential for fluid therapy to help starts to diminish. Fluid can leak from the capillaries as fast as it is administered. In addition, severe sepsis often presents with high blood flow states. The problem is not a lack of fluid, but of maldistribution of blood flow due to microcapillary obstruction. When fluid is given, an oxygen end point (e.g., SvO2) helps determine when fluid therapy is beneficial.

Replacement Dose Steroids – Adrenal insufficiency occurs in between 25% and 40% of patients with septic shock and is indicated by the need for vasopressors. Appropriate dosing of steroids provides support to dysfunctional adrenal glands and enhances vasomotor tone. Physiologic doses of intravenous steroids (200 to 300 mg/day for 7 days) in patients with relative adrenal insufficiency who were in septic shock achieved significant shock attenuation and mortality reduction. Earlier studies from the 1980s tested doses greater than 300 mg/day and showed that steroids were not only ineffective, but also potentially detrimental in sepsis treatment. It is not clear how to best diagnose adrenal insufficiency, e.g., total cortisol levels, adrenocorticotropic hormone (ACTH) testing. However, replacement dose steroid treatment for patients who require vasopressors is a logical step at this time.

Intensive Insulin Therapy – Insulin therapy to maintain blood glucose levels at 80 to 110 mg/dL has also been shown to reduce morbidity and mortality among critically ill patients undergoing surgery, compared to conventional therapy that maintained blood glucose at 180 to 200 mg/dL. Intensive insulin therapy reduced the incidence of septic episodes by 46% and decreased mortality (12.5%) among patients with bacteremia compared to patients who received conventional therapy (29.5%).

Vasopressor Therapy – The goal of vasopressor therapy is to increase vascular constriction, leading to improved perfusion. However, failure of the capillaries and poor oxygen delivery to the cells are not resolved by this treatment. In severe sepsis studies the need for vasopressors was associated with a high risk of mortality (Figure 7). In the placebo group, the mortality rate of patients who did not receive a vasopressor was 20%. In patients who received a low-dose vasopressor, the mortality rate was 37%, and in patients who received high-dose vasopressors, the mortality rate was 58%. Use of escalating doses of vasopressors may be a proxy for increases in the severity of the sepsis. Therefore, increased use of vasopressors should be an indicator that severe sepsis is worsening.

CAMPAIGN RECOMMENDATIONS FOR THE TREATMENT OF SEVERE SEPSIS AND SUBSEQUENT ORGAN DYSFUNCTION

Immediate Care
1. Rapid response with a goal of restoring systemic balance can reduce the overall mortality rate of patients with severe sepsis. Resuscitation of a patient in severe sepsis or septic shock must begin as soon as the syndrome is recognized, and all patients should be evaluated for severe sepsis within 2 hours of admission to the ICU. Serum lactate measurements must be obtained to detect occult hypoperfusion (>4 mmol/L), which is a significant indicator of organ dysfunction, possibly suggesting the onset of severe sepsis. During the first 6 hours of resuscitation, the treatment protocol should be directed with a goal of achieving central venous pressure of 8 to 12 mm Hg (12 to 15 mm Hg for patients on mechanical ventilation), mean arterial pressure...
Shock Management

1. Should fluid resuscitation fail to restore adequate blood pressure and organ perfusion, vasopressor agents should be instituted. Vasopressors also may be used on an emergency basis in patients with life-threatening hypotension or severe shock. Either norepinephrine or dopamine, administered through a central catheter, is the first-choice vasopressor agent to correct hypotension.36-41 Low-dose dopamine should not be used as it has not been shown to be beneficial in restoring renal function.42,43

2. Dobutamine is advocated as a measure to increase cardiac output in patients who do not respond to fluid resuscitation. When used in patients with low blood pressure, it should be combined with vasopressor therapy.44 However, patients do not benefit from increasing oxygen delivery to supranormal levels, and the goal should be achieving adequate oxygen delivery.45,46

3. Low-dose steroids are recommended in patients with septic shock requiring vasopressors to maintain adequate blood pressure.25-27

4. There is no evidence to support the use of bicarbonate therapy for treatment of hypoperfusion-induced lactic acidemia with pH of 7.15 or lower. In trials, there was no evidence that bicarbonate improved hemodynamics or reduced the need for vasopressors.47,48

Ventilation

1. High plateau pressures greater than 30 cm H2O should be avoided in patients on mechanical ventilation as a result of acute lung injury or acute respiratory distress syndrome.49 The recommendation of the Surviving Sepsis Campaign is to employ prone positioning for patients who require high levels of FiO2 and are not at high risk for problems associated with positional change.50,51 For other patients requiring mechanical ventilation, the recommendation is to raise the head of the bed 45° to reduce the incidence of pneumonia.52

2. Permissive hypercapnia, allowing PaCO2 to increase above normal, can be tolerated to minimize plateau pressures and tidal volumes without increasing mortality in patients, but should not be considered for patients following head trauma. Hypercapnia has been shown to increase heart rate, blood pressure, and cardiac output.53,54

3. Patients receiving mechanical ventilation should undergo spontaneous breathing trials to determine when they may be

(MAP) ≥ 65 mm Hg, urine output ≥ 0.5 mL/kg/hour, and SVO2 levels ≥ 70%. If sufficient SVO2 cannot be achieved through fluid resuscitation, a transfusion of packed red blood cells to achieve a hematocrit of 0.30 or greater and/or administration of a dobutamine infusion up to 20 mcg/kg/min should be employed to reach this goal.

2. The Surviving Sepsis Campaign determined there was no evidence-based support that favored either natural or artificial colloids or crystalloids for fluid resuscitation, so either option is appropriate.33-35 One consideration is that resuscitation with crystalloids requires more fluid and, therefore, results in more edema.

3. Within 1 hour of a presumptive diagnosis, cultures must be obtained, preferably at least one obtained percutaneously and one through each lumen of each vascular access device. Cultures from blood, urine, cerebrospinal fluid, wounds, respiratory secretions, or other bodily fluids should be obtained before antibiotics start as the clinical presentation dictates. Starting antibiotics must be made a top priority, so empiric treatment should be started on a presumptive diagnosis and should be selected to cover the broadest spectrum of activity. When the culture data are available, antibiotic therapy can be refined to a narrower spectrum to avoid development of a superinfection or resistant organisms.18

No Vasopressor to Low Dose

No Vasopressor to High Dose

Vasopressor as a Marker for Severe Sepsis with High Risk of Death

Copyright © 2003, Eli Lilly and Company. All rights reserved. Printed with permission.
extubated. Before trials are initiated, patients should be arousable, hemodynamically stable without vasopressor agents, have no new potentially serious conditions, and be able to receive supplemental oxygen safely through a facemask or nasal cannula. These spontaneous trials may reduce the duration of mechanical ventilation.55,56

4. Goals and a standardized sedation scale should be established when sedation is necessary for patients receiving mechanical ventilation, and daily interruptions or lightening of sedation should be scheduled when possible. Patients who have sedation interruptions have been shown to have significantly shorter ventilation periods, as well as shorter stays in the ICU and in the hospital.57

5. Neuromuscular blockers should be avoided in patients with sepsis because there is a risk of prolonged neuromuscular blockade after the drugs have been discontinued. Use of neuromuscular blockers beyond the first few hours of mechanical ventilation has been associated with prolonged skeletal muscle weakness58-65 and may lead to longer periods of paralysis.66,67

**Severe Sepsis Management**

1. Patients presenting with severe sepsis should be evaluated for areas of infection where source control measures, such as draining an abscess or debriding infecting necrotic tissue, may remove the infection source.68 If such measures do not pose further risk to the patient, they should be performed following appropriate resuscitation.69

2. Xigris is recommended for patients at high risk for death, such as an APACHE II score of 25 or greater, sepsis-induced multiple organ failure, septic shock, or sepsis-induced acute respiratory distress syndrome, if the patient has no absolute contraindications related to bleeding risk.23

**Glucose Control**

1. After the initial stabilization of patients with severe sepsis, blood glucose levels should be maintained at 150 mg/dL or lower, with the optimal blood glucose levels being between 80 and 110 mg/dL.70,71 In patients in whom continuous infusion of insulin and glucose is used to maintain control, glucose should be monitored frequently after initiation (every 30 to 60 minutes) and on a regular basis (every 4 hours) once the glucose level has stabilized.

**BUNDLING RECOMMENDATIONS**

The campaign's guidelines made no attempt to prioritize or formulate a hierarchy of interventions. To make a cumbersome list of endorsements more clinically applicable, a “bundling” system has been proposed by the Institute of Healthcare Improvement to encourage change in practice.72 It is important to note that these bundled interventions have not yet been studied for clinical efficacy or workability. They are merely a possible checklist for instituting the guidelines in a user-friendly manner.

The bundles were divided into 4 groups: 4 hours and 24 hours without shock, and 4 hours and 24 hours with shock. Recently the recommendations have been revised to 6-hour and 24-hour bundles.

**6 hours without shock:**
- Presumptive diagnosis within 2 hours of patient admission
- Serum lactate measurement (occult hypoperfusion >4 mmol/L)
- Cultures and empiric antibiotics within 1 hour of presumptive diagnosis

This bundle emphasizes that in the case of sepsis, a delay in treatment significantly increases risk of mortality. Antibiotics are life-saving and broad-spectrum agents must be given before culture results are available. Later when laboratory results are finalized, antibiotic therapy can be fine-tuned. This bundle also illustrates that hypoperfusion can be present despite seemingly acceptable vital signs. The presence of an elevated lactate level reveals the microcirculatory disruption and cellular hypoxia of sepsis. It also implies a need for fluid resuscitation (see 6 hours with shock bundle).

**24 hours without shock:**
- Maintain glucose <150 mg/dL.
- For patients receiving mechanical ventilation: tidal volume ~6 mL/kg of lean body weight; plateau pressure <30 cm H2O
- Administration of Xigris, using local guidelines

Rapid response with a goal of restoring systemic balance can reduce the overall mortality rate of patients with severe sepsis. Resuscitation...must begin as soon as the syndrome is recognized...
This bundle focuses on research done by van den Berghe et al \(^{32}\) on the survival benefits of glucose control in surgical patients, as well as multiple studies supporting lung protection strategies for patients with acute respiratory distress syndrome, a frequent companion of sepsis. In addition, Xigris’s anti-inflammatory, anticoagulant, and fibrinolytic effects are highlighted for microcirculatory improvement and organ perfusion support.

6 hours with shock:
- Presumptive diagnosis within 2 hours
- Cultures and empiric antibiotics within 1 hour of presumptive diagnosis
- Fluid resuscitation (crystalloid or colloid)
- Vasopressors for patients with mean arterial pressure <65 mm Hg during and after fluid treatment
- Central venous pressure (CVP) line placement if blood pressure is unresponsive to fluids or serum lactate levels are elevated
- Administration of inotropes (dobutamine up to 20 mcg/kg/min) and/or packed red blood cells (hematocrit of >0.30) for central venous oxyhemoglobin saturation (ScVO\(_2\)) <70%
- Steroids for septic shock requiring continued use of vasopressors

This bundle relates to the hemodynamic support of septic shock. Endotoxin, exotoxin, and the multiple chemical mediators involved in sepsis lead to widespread inflammation, causing injury to vascular endothelium throughout the body. The damaged vessels become dilated and leak, leading to vaso- and hypovolemic forms of shock. Additionally, this chemical storm can be traumatic for the heart, adding a cardiogenic component.

While resuscitating vascular volume, the choice of fluid appears to make no difference in outcome, so either crystalloids or colloids may be utilized. The remaining recommendations in this bundle are based on the Early Goal-Directed Therapy trial, which dealt with the resuscitation of septic patients with hypotension or lactic acidosis.\(^{19}\) In addition to blood pressure and urinary output guidelines, the study’s successful end points for resuscitation included preload values targeting a higher than usual central venous pressure and the tracking of central venous oxygen saturation as a marker of overall oxygen balance, maintain:
- CVP 8-12 mm Hg (12-15 mm Hg if on ventilator)
- MAP \(\geq 65\) mm Hg

### Case Study 1

A 64-year-old man is admitted to the surgical ICU following a motor vehicle accident. The patient’s progress is unremarkable until postoperative day 5. In his examination on day 5, his clinical presentation is detailed below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>39.2°C</td>
</tr>
<tr>
<td>FiO(_2)</td>
<td>60%</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>450 cc</td>
</tr>
<tr>
<td>Positive end-expiratory pressure</td>
<td>+10 cm H(_2)O</td>
</tr>
<tr>
<td>SpO(_2)</td>
<td>88%</td>
</tr>
<tr>
<td>PaO(_2)</td>
<td>56 mm Hg</td>
</tr>
<tr>
<td></td>
<td>(P/F ratio = 100)</td>
</tr>
<tr>
<td>pH</td>
<td>7.31</td>
</tr>
<tr>
<td>PaCO(_2)</td>
<td>33 mm Hg</td>
</tr>
<tr>
<td>HCO(_3)</td>
<td>18 mmol/L</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>110/50 mm Hg (with 20 mcg/kg norepinephrine (Levophed, Sanofi))</td>
</tr>
<tr>
<td>Heart rate</td>
<td>122 beats/minute</td>
</tr>
<tr>
<td>White blood cells</td>
<td>13 800/mm(^3)</td>
</tr>
<tr>
<td>Platelets</td>
<td>130 000/mm(^3)</td>
</tr>
</tbody>
</table>

**Is there evidence of an infection?**
Yes. It is not clear if ventilator-associated pneumonia is present, but infection should be suspected.

**Does this patient have sepsis?**
Yes. There is evidence of infection, he has tachycardia, tachypnea, elevated white blood cell count, and elevated temperature, so SIRS is present, and when coupled with infection, this is sepsis.

**Does this patient have severe sepsis?**
Yes. The tachypnea, elevated FiO\(_2\), decreased PaO\(_2\), and P/F ratio suggest significant lung dysfunction. The patient also is tachycardic and is taking a vasopressor, suggesting cardiovascular dysfunction.

**What would be appropriate care for this patient?**
This patient is a candidate for Xigris, based on the FDA indications of significant risk of mortality, because he has failure of 2 organs (40% chance of mortality) and is taking a vasopressor (32% chance of mortality). He is receiving vasopressor therapy, a grade E recommendation by the Surviving Sepsis Campaign, but not Xigris, a grade B recommendation. Although this is a postsurgical patient, the risk of bleeding as a result of Xigris is small.
• Urine Output ≥ 0.5 mL/kg/hr
• ScvO₂ ≥ 70%

This bundle includes additional suggestions for maintaining adequate hemodynamics through inotropic support and blood transfusions. Oxygen deficit must be addressed early in sepsis before cells succumb to refractory hypoperfusion and organ failure. Vasopressors are included for the treatment of refractory hypotension, but critical care personnel must understand that there is a fine line between constricting vessels to create pressure and cutting off blood flow. Either dopamine or norepinephrine may be appropriate vasopressors for sepsis, but low-dose dopamine for renal protection should not be employed. Vasopressin may be considered for patients not responding to conventional vasopressors, but it should not be increased beyond 0.04 units/minute.

This bundle includes an endorsement of low-dose steroids

CASE STUDY 2

A 48-year-old woman presents in the emergency department with “difficulty shaking a cold.” She has a long-term history of smoking, allergies, and chronic bouts of bronchitis. She has had a productive cough for 2 weeks and is complaining of weakness and feeling “run down.” She has rhonchi and wheezes in both lung fields, and multiple small red lesions are noted on both legs. Her vital signs:

<table>
<thead>
<tr>
<th>Temperature</th>
<th>38.7°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td>24 breaths/minute</td>
</tr>
<tr>
<td>Heart rate</td>
<td>102 beats/minute</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>92/62 mm Hg</td>
</tr>
</tbody>
</table>

Is there evidence of an infection?
Yes. The temperature elevation is an obvious sign.

Does this patient have sepsis?
Yes. There is evidence of infection and the tachycardia, tachypnea, and elevated temperature are SIRS, so this patient has sepsis.

Does this patient have severe sepsis?
Yes. The patient is tachycardic and relatively hypotensive, something that could easily be attributed to simple hypovolemia; regardless, these are signs of organ dysfunction. More importantly, the red lesions suggest purpura fulminans, an ominous sign indicating hematologic dysfunction, most likely disseminated intravascular coagulation. She is at risk of perfusion defects, including potential limb loss.

What would be appropriate care for this patient?
Fluid therapy for her hemodynamic compromise should be initiated. A sputum culture, blood culture, coagulation profile, and lactate level should be obtained and immediately followed by empiric antibiotic therapy. She should be closely monitored and evaluated for Xigris if she does not respond satisfactorily to fluid resuscitation.

CASE STUDY 3

An 80-year-old man with benign prosthetic hypertrophy had a foley catheter placed 9 days ago and was sent home to await a transurethral prostate resection. He is now reporting to the outpatient surgery center for his procedure. He is attended by his daughter. She states that the patient’s urinary output has dwindled in the past 3 days and that he seems tired and has been sleeping more than usual. His urine output is low, and what is produced is cloudy and concentrated. In the surgery center, he seems lethargic. His vital signs:

<table>
<thead>
<tr>
<th>Temperature</th>
<th>38.6°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td>26 breaths/minute</td>
</tr>
<tr>
<td>Heart rate</td>
<td>122 beats/minute</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>82/50 mm Hg</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>3700/mm</td>
</tr>
</tbody>
</table>

Is there evidence of an infection?
Yes. He has a low-grade fever and cloudy urine.

Does this patient have sepsis?
Yes. The elevated temperature, decreased white blood cell count, tachycardia, and tachypnea meet the SIRS criteria, and SIRS plus infection meets the definition of sepsis.

Does this patient have severe sepsis?
Yes. Evidence of organ dysfunction includes hypotension, tachycardia, and lethargy. He may also be in renal failure.

What would be appropriate care for this patient?
Surgery must be postponed until the patient’s condition improves. Urine and blood cultures and a renal panel are indicated. Fluid therapy is appropriate and would best be guided by central venous pressure monitoring (early, goal-directed therapy) due to the patient’s age. Antibiotics should be started within the hour. If vasopressors prove necessary for hemodynamic support, Xigris should be considered.
(rather than the ineffective high-dose therapy of the 1980s) for patients requiring vasopressor support. Intravenous steroids at 200 to 300 mg/day for 7 days, evaluated by Annane, et al, attenuated shock and reduced mortality in patients with relative adrenal insufficiency.28 As always, the use of steroids is controversial and this strategy is only a grade C recommendation.

24 hours with shock:
- Maintain glucose <150 mg/dL
- For patients receiving mechanical ventilation, tidal volume ~6 mL/kg of ideal body weight; plateau pressure <30 cm H2O
- Administration of Xigris

The next phase of the Surviving Sepsis Campaign is to implement the committee’s bundled core recommendations in critical care settings where the clinical impact can be measured.

CONCLUSION

Patients with severe sepsis and septic shock are among the most critically ill in the ICU. Once the cycle of inflammation and coagulation begins, it is difficult to halt, and nurses are left to witness a patient’s downward spiral into organ failure and death. Critical care nurses play a vital role in preventing sepsis and severe sepsis by identifying patients at risk early in the development of the condition, which can significantly increase chances of survival.

In cases where severe sepsis occurs, the Surviving Sepsis Campaign offers hope for a unified and standardized approach to patient care. Critical care nurses must familiarize themselves with the new guidelines and serve as change agents in establishing systems for adopting them into their unit protocols.

References

CASE STUDY 4

A 36-year-old man on the medical-surgical floor has been receiving an intravenous antibiotic for 36 hours for a wound on his left foot. The wound was obtained 1 week earlier while he was fishing in a local river. He attempted to manage it at home, but it advanced to cellulitis of his entire calf. His first day in the hospital was uneventful. Outside of fever (38.2°C to 38.9°C), his vital signs were stable. On the second day, he was agitated and slightly confused, after having been pleasant and cooperative previously. His vital signs:

| Temperature | 36.3°C |
| Respiration | 28 breaths/minute |
| Heart rate | 112 beats/minute |
| Blood pressure | 140/62 mm Hg |
| SpO2 | 90% on room air |

Is there evidence of an infection?

Yes. He has a history confirming the presence of infection and he is on antibiotics. Currently, there is no temperature elevation, and one might be tempted to believe that the patient is improving with therapy. Comparing patient data from 1 set of readings to another is important. This patient had a temperature between 38.2°C and 38.9°C on day one. His heart rate had been in the upper 80s and his respiratory rate had been less than 20 breaths per minute since admission. There was no previous SpO2, but a baseline admission blood gas showed an SaO2 of 96%.

Does this patient have sepsis?

Yes. This patient has an infection and shows signs of tachycardia and tachypnea (SIRS). The temperature change is also reason for concern.

Does this patient have severe sepsis?

Yes. His vital sign changes overnight indicate possible deterioration in regard to cardiac and respiratory function. Of particular concern is the change in level of consciousness. Agitation could explain the vital sign changes, but why would a 36-year-old become agitated and confused?

What would be appropriate care for this patient?

A lactate level should be obtained immediately. If it is greater than 4 mmol/L (occult hypoperfusion), fluid therapy should be initiated despite the adequate blood pressure. Cultures and sensitivities must be checked and antibiotics reevaluated for efficacy. As he appears to be having respiratory difficulty, a chest film may be indicated along with low-dose oxygen therapy. Continue close observation and initiate appropriate treatments if hypoperfusion is present.
Surviving Severe Sepsis:
Early Recognition and Treatment

Objectives:
1. Identify the signs of systemic inflammation
2. Distinguish among the sepsis identification definitions
3. Discuss the components of the new Surviving Sepsis Campaign guidelines
4. Describe essential aspects of treatment for severe sepsis

Mark your answers clearly in the appropriate box. There is only 1 correct answer. You may photocopy this form.

1. [ ] a 2. [ ] a 3. [ ] a 4. [ ] a 5. [ ] a 6. [ ] a 7. [ ] a 8. [ ] a 9. [ ] a 10. [ ] a 11. [ ] a 12. [ ] a 13. [ ] a 14. [ ] a 15. [ ] a

Objective 1 was met
Objective 2 was met
Objective 3 was met
Objective 4 was met
The content was appropriate
My expectations were met
This method of CE is effective for this content

The level of difficulty of this test was:
[ ] easy  [ ] medium  [ ] difficult
To complete this program, it took me ___ hours / minutes.

Name ____________________________
Address __________________________
City ____________________________  State _____  ZIP ___________
Phone (___) ____________
E-mail address __________________________
AACN member number __________________________
[ ] I would like to receive my certificate via e-mail (check box)

Mail this entire page to AACN, 101 Columbia, Aliso Viejo, CA 92656, (800) 899-2226
1. All of the following are criteria for assessing a patient for the presence of sepsis except?
   a. Blood pressure > 110/80
   b. Heart rate > 90 beats/minute
   c. White blood cell count > 12 000/mm³ or < 4000 mm³
   d. Core temperature >38°C or <36°C

2. Which of the following terms is given to sepsis plus 1 or more organ dysfunction?
   a. Infection
   b. Systemic inflammatory response
   c. Septic shock
   d. Severe sepsis

3. What is the risk of death from severe sepsis with 2 organ failures?
   a. 20%
   b. 40%
   c. 60%
   d. 80%

4. When high-dose vasopressor therapy was used with patients with severe sepsis in the PROWESS trial, what was the chance of mortality?
   a. 25%
   b. 37%
   c. 46%
   d. 58%

5. The goal of the Surviving Sepsis Campaign is to reduce mortality caused by sepsis by what percent within 5 years?
   a. 5%
   b. 10%
   c. 15%
   d. 25%

6. Which of the following statements about the Surviving Sepsis Campaign is not true?
   a. The campaign addresses the use of paralytics and renal replacement therapy.
   b. The campaign includes recommendations about prophylaxis for stress ulcers.
   c. The campaign only addresses patients with severe sepsis.
   d. The campaign suggests daily interruptions for patients undergoing sedation, when possible.

7. What grade of treatment recommendation is associated with the highest level of scientific evidence?
   a. Grade A
   b. Grade B
   c. Grade C
   d. Grade D

8. Which of the following symptoms are not associated with organ dysfunction in a patient with sepsis?
   a. Tachycardia
   b. Hypotension
   c. Confusion or lethargy
   d. Persistent cough

9. When fluid resuscitation begins, what is the minimal target urine output?
   a. 0.1 mL/kg/hour
   b. 0.25 mL/kg/hour
   c. 0.5 mL/kg/hour
   d. 1.0 mL/kg/hour

10. When should antibiotic therapy be initiated if an infection is suspected?
    a. After waiting to determine response to fluid resuscitation
    b. Immediately after obtaining cultures from blood and other bodily fluids
    c. Before culturing the patient’s blood and bodily fluids
    d. After 12 to 24 hours of observation

11. In the PROWESS trial, use of activated protein C resulted in what percent decreased mortality in patients with severe sepsis who had a high risk of death?
    a. 1%
    b. 5%
    c. 10%
    d. 13%

12. In the PROWESS trial, what was the risk of serious bleeding associated with use of activated protein C?
    a. 3.5%
    b. 5%
    c. 11.5%
    d. 21%

13. Early goal-directed therapy is recommended for institution within what time frame of the diagnosis of severe sepsis?
    a. 3 hours
    b. 6 hours
    c. 9 hours
    d. 12 hours

14. What level of serum lactate signifies occult hypoperfusion?
    a. <1 mmol/L
    b. 1-2 mmol/L
    c. 2-3 mmol/L
    d. >4 mmol/L

15. Which of the following interventions is not indicated within 6 hours of septic shock?
    a. Maintaining glucose control
    b. Cultures
    c. Empiric antibiotics
    d. Fluid resuscitation
Surviving Severe Sepsis: Early Recognition and Treatment
Tom Ahrens and Deborah Tuggle

Crit Care Nurse 2004;24 S2-S13
©2004 American Association of Critical-Care Nurses
Published online http://ccn.aacnjournals.org/

Personal use only. For copyright permission information:
http://ccn.aacnjournals.org/cgi/external_ref?link_type=PERMISSIONDIRECT

Subscription Information
http://ccn.aacnjournals.org/subscriptions/

Information for authors
http://ccn.aacnjournals.org/misc/ifora.xhtml

Submit a manuscript
http://www.editorialmanager.com/ccn

Email alerts
http://ccn.aacnjournals.org/subscriptions/etoc.xhtml