Major advances are occurring in healthcare, and critical care is no exception. For example, a drug now exists that works to treat severe sepsis, the leading cause of death in noncardiac intensive care units (ICUs)\(^1\) (Table 1). In 2001, the United States Food and Drug Administration approved the use of Xigris (drotrecogin alfa [activated], Eli Lilly and Co, Indianapolis, Ind), a recombinant form of human activated protein C, to reduce mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (eg, as determined by the Acute Physiology and Chronic Health Evaluation [APACHE] II).\(^4\)

Xigris is the first drug shown to improve survival in severe sepsis. The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, which evaluated Xigris, was a large double-blind, placebo-controlled, international study. Xigris treatment was associated with a 6.1% absolute reduction in mortality and a 19.4% reduction in the relative risk of death (\(P<.005\)).

Before Xigris became commercially available, it was widely anticipated that use of the drug would be widespread in most ICUs; however, the use of Xigris so far has been modest. Why has the use of a therapy shown to improve survival in a previously untreatable disease been slow? Four major barriers are most likely decreasing use of this drug: (1) failure to diagnose high-risk severe sepsis and determine which patients are appropriate candidates for treatment, (2) lack of understanding of the data supporting the efficacy of the drug, (3) failure to understand and manage bleeding risk in patients with sepsis, and (4) the cost associated with a novel treatment.

To help address these issues, we review the incidence and pathophysiology of severe sepsis, paying particular attention to the appropriate use and the current challenges to the use of Xigris. By applying a better understanding of severe sepsis and the appropriate use of Xigris, clinicians may be able to reduce the mortality rate of severe sepsis in many ICUs.
INCIDENCE OF SEVERE SEPSIS

One of the challenges associated with severe sepsis is that it is commonly underrecognized. When someone is reported to have died of pneumonia, they may really have died of an overwhelming failure of multiple organs due to the infection, that is, severe sepsis. This type of understanding is essential because underrecognition typically means inappropriate treatment. The incidence of severe sepsis is striking when compared with the incidences of other common clinical conditions (Figure 1). Ultimately, severe sepsis must be recognized rapidly in order for proper therapy to be initiated.

PATHOPHYSIOLOGY OF SEVERE SEPSIS

The pathophysiology of severe sepsis must be understood in order to use new therapies appropriately. A brief overview of the pathophysiology of severe sepsis is provided here in order to clarify why previous therapies often have not worked well and why Xigris has proven effective.

Many derangements in homeostasis occur with severe sepsis. Evidence suggests that disturbances in the inflammation, coagulation, and fibrinolytic systems occur in severe sepsis. The proinflammatory and procoagulation responses dominate and lead to uncontrolled systemic inflammation and advanced coagulopathy. Three known problems occur with this response: 1. excess coagulation, 2. exaggerated or malignant inflammation, and 3. impaired fibrinolysis.

A review of the normal immune response to infection helps provide a framework to understand what happens in severe sepsis (Figure 2). When an antigen enters the bloodstream, it is sensed, usually by circulating monocytes or neutrophils, and an immune response is initiated. Monocytes release inflammatory mediators and tissue factor that start a series of events that progresses very rapidly. Tissue factor initiates the coagulation cascade, causing thrombin to convert fibrinogen to fibrin, leading to the development of a fibrin clot. This clot formation in the microvasculature may be an attempt by the immune system to seal the antigen off in a relatively small part of the body. In the absence of infection, endogenous tissue plasminogen activator will break down the clot. With an infection, plasminogen activator inhibitor-1 and thrombin activatable fibrinolysis inhibitor are released; these factors suppress fibrinolysis and allow the clot to remain. With the infecting antigen trapped, the immune system acts to destroy it.

Several things happen to destroy the invading antigen. The endothelial membrane is altered, resulting in increased capillary permeability and allowing neutrophils to enter the area. In addition, E-selectin and P-selectin are activated so that neutrophils do not roll past but are grabbed and held in place. These neutrophils destroy antigens by several mechanisms. One of these is called a respiratory burst, which is the release of oxygen radicals into the environment immediately around the antigen. Oxygen radicals are oxygen molecules that have 6 instead of 8 electrons. With 6 electrons, oxygen is very unstable and

![Graph: Incidence of Severe Sepsis vs. Other Conditions](http://ccn.aacnjournals.org/Downloaded from http://ccn.aacnjournals.org/ by AACN on October 23, 2017)
Molecules that lose their electrons to oxygen become unstable. The presence of a few oxygen radicals is not significant, but increased amounts can literally cause such molecular instability that the cell wall disintegrates. Although the neutrophil has other mechanisms for destroying antigens, the respiratory burst is extremely powerful.

In severe sepsis, the reaction to an infection does not stay localized; this remains one of the fundamental mysteries associated with the disease. The excess inflammation and coagulation spreads throughout the body, possibly because the infection has gotten into the systemic bloodstream or because of collateral damage associated with the immune response (e.g., excessive damage due to oxygen radicals). Any and all organs can be affected by excess coagulation, impairment in fibrinolysis, and excess inflammation. Several theories, including genetic predisposition, have been suggested to explain why the immune response becomes systemic in some patients. Regardless of the cause, it is clear that by the time severe sepsis is clinically recognized, it is already affecting large areas of the body.

Widespread fibrin deposition interferes with blood flow and threatens tissue oxygenation. Blood flow to organ tissue can be reduced despite adequate cardiac output because of the microvascular disturbances associated with the immune response and the imbalance between coagulation and fibrinolysis.

**TISSUE PERFUSION AND OXYGEN DELIVERY IN SEVERE SEPSIS**

If blood flow or tissue perfusion is reduced, tissue nutrition (including oxygenation) may be disrupted, with serious consequences. It is very difficult in clinical practice to assess the impact of decreased perfusion. In order to assess the effects of impaired blood flow, measures of tissue oxygenation are necessary. The most common clinical indicator of blood flow and perfusion is blood pressure, but arterial blood pressure is, at best, an indirect indication of peripheral blood flow. For example, a patient may have a normal blood pressure and still have reduced blood flow in various capillary beds because of regional vasosstriction. Also, a patient with a low blood pressure can have a cardiac output that is either high or low, again depending on the presence of vasodilatation or vasostriction. The essential variable for patients with severe sepsis is not necessarily blood pressure, but oxygen delivery to the tissue (tissue oxygenation).

One effective, but invasive, measure of tissue oxygenation is the oxygen saturation in central venous or mixed venous blood (SvO₂). The SvO₂ reflects the amount of oxygen left in the blood after the blood has passed through the capillary beds, that is, the amount of oxygen still bound to hemoglobin in the venous circulation. This global reflection of tissue oxygenation has value in severe sepsis because of the systemic nature of the disease. Consideration of SvO₂ can provide understanding of severe sepsis at the tissue level.

A normal SvO₂ is about 60% to 75%, meaning that normally only 25% to 40% of oxygen available in the blood is extracted by the tissues to support metabolism. If tissues require more oxygen, the body can either increase the cardiac output or extract more oxy-
gen from the hemoglobin. Also, if the rate of blood flow through a tissue bed is reduced, the tissue can meet its needs by extracting a higher percentage of the available oxygen and thus reducing \( S\text{\textsubscript{\(\text{vO}_2\)}} \). Conversely, a higher blood flow with the same oxygen demand will normally result in an increased \( S\text{\textsubscript{\(\text{vO}_2\)}} \). Generally speaking, a lower \( S\text{\textsubscript{\(\text{vO}_2\)}} \) indicates that more of the available oxygen in the blood is being extracted by the tissues. In severe sepsis, the \( S\text{\textsubscript{\(\text{vO}_2\)}} \) can either be low or high.\(^{12}\) An increased \( S\text{\textsubscript{\(\text{vO}_2\)}} \) during severe sepsis reflects the impact of microcirculatory (capillary) obstruction due to excess coagulation and impaired fibrinolysis.

Proper tissue oxygenation is reflected by a normal blood pressure and a normal \( S\text{\textsubscript{\(\text{vO}_2\)}} \). Critically ill patients commonly face 3 threats to tissue oxygenation:

1. **Left ventricular dysfunction**
   a. myocardial infarction
   b. congestive heart failure
   c. cardiomyopathy

2. **Hypovolemia**
   a. postoperative bleeding
   b. gastrointestinal bleeding
   c. trauma

3. **Sepsis**

In left ventricular dysfunction and hypovolemia, both associated with low cardiac output, it is rare to find an elevated \( S\text{\textsubscript{\(\text{vO}_2\)}} \). As blood flow decreases, tissues extract more oxygen, causing the \( S\text{\textsubscript{\(\text{vO}_2\)}} \) to decrease. In sepsis, however, the blood often returns to the lungs with elevated \( S\text{\textsubscript{\(\text{vO}_2\)}} \) levels. The inability for the tissues to receive, or perhaps use, oxygen causes these high \( S\text{\textsubscript{\(\text{vO}_2\)}} \) levels. Blood flow is increased in severe sepsis, yet tissue oxygenation continues to suffer despite normal or high cardiac output.

**RECOGNIZING SEVERE SEPSIS**

Timely and effective recognition of severe sepsis is limited by many factors. Many clinicians wait for signs of multiple organ dysfunction before considering therapy with Xigris. This delay may be too long, because dysfunction of a single organ most likely indicates that oxygen and nutrient delivery to the tissues has been insufficient for some time. Also, by the time 1 organ is showing signs of dysfunction, it is highly likely that other organs are already affected but have not yet begun to show overt signs of dysfunction. To prevent avoidable delays in recognizing severe sepsis, nurses must be skilled at recognizing dysfunction of any organ. The most common organs to show signs of dysfunction are those in the cardiovascular and pulmonary systems, but any organ can fail. Figure 3 lists symptoms commonly associated with dysfunction in each of the major organ systems, including renal, hepatic, hematologic, and central nervous system dysfunction.

The definition of severe sepsis has not always been clear, and the determination of which patients with severe sepsis may benefit from novel treatments like Xigris is not always easy. In the future, a blood test may be available to help clinicians detect severe sepsis, much like the test we have now for detecting myocardial infarction (eg, measuring the troponin level). In the meantime, what is the best strategy for recognizing severe sepsis? Perhaps the simplest guidelines are those originally developed at a consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine (Table 2).\(^{14,15}\) Another consensus conference occurred more recently but did not make substantial changes to the original recommendations (Table 3).\(^{16}\) Ultimately, the diagnosis of severe sepsis requires 3 things:

1. The patient must have a known or suspected infection.
2. At least 2 signs of systemic inflammatory response syndrome (SIRS) should be present, indicating a systemic response to the infection. The patient may have tachycardia, tachypnea, or
an elevated or decreased body temperature. The white blood cell count is typically increased in patients with sepsis; however, in some patients, the white blood cell count is decreased or within normal limits with a differential count that shows an increased number of immature neutrophils (bands). If at least 2 of these criteria are met, the patient most likely has sepsis.

3. At least 1 organ must be failing or dysfunctional.

The most common organs that fail are those in the cardiovascular and pulmonary systems. Cardiovascular dysfunction is present if the patient requires a vasopressor (eg, norepinephrine or dopamine) to maintain the blood pressure, provided that an adequate fluid challenge has been administered. Accumulating evidence suggests that simply requiring either low or high doses of vasopressors is associated with a 30% to 50% increased chance of death17 (Figure 4).

Pulmonary dysfunction is present if a patient requires a fraction of inspired oxygen (FiO₂) of 0.50 and has oxygen saturation measured by pulse oximetry values of less than 95%, or a PaO₂ less than 100 mm Hg. More sophisticated measures of pulmonary function may be used, for example, measurement of the intrapulmonary shunt (Q_s/Q_t or the PaO₂/FiO₂ ratio), but they essentially confirm the FiO₂ and pulse oximetry guidelines just described. It is imperative that nurses, who are usually the first clinicians to observe that a patient’s condition is worsening, be skilled at recognizing the signs of severe sepsis. If 1 organ system starts to fail, others are likely to follow. The presence of multiple dysfunctional organs is most likely one of the reasons that mortality rates in severe sepsis range from 20% to 80%. As more organs fail, mortality rates increase substantially (Figure 5). Therefore, bedside nurses need a tool to help recognize severe sepsis early. Patients receiving antibiotics, a vasopressor, and/or mechanical ventilation consistently meet the criteria for severe sepsis with a high risk of death. A mnemonic called APEX or Antibiotics, Pressors, Evaluate for treatment with Xigris can help bedside nurses to evaluate patients progressing along the sepsis continuum. At this time, Xigris is approved for use in adult patients with severe sepsis (sepsis with acute organ dysfunction and at least 1 organ dysfunction).
dysfunction), who are at a high risk of death. Before Xigris became available, most treatment options available for patients with severe sepsis were supportive and had been in use for decades, (ie, administration of antibiotics, fluids, and vasopressors).

**TREATMENT OF SEVERE SEPSIS**

Surviving severe sepsis has to do with recovering function at the microcirculatory level so that dysfunctional organs can begin to function again. This situation is one of the reasons that antibiotics have limited ability to cure severe sepsis. Although control of the source of the infection is imperative and appropriate use of antibiotics is essential, severe sepsis involves a disturbance in the immune system’s response to the original infection (Figure 6). Antibiotics do not treat the immune system response to the infection and are therefore limited in their ability to help patients with severe sepsis. Additionally, antibiotics do not directly improve tissue perfusion or the associated delivery of oxygen and nutrients. In severe sepsis, the patient has excess coagulation and inflammation and impaired fibrinolysis with disruption of the endothelial layer. The endothelial wall disruption includes markedly increased capillary permeability and venodilatation. This disturbance in the endothelial wall is the basis for the next 2 routine therapies.

**Fluid Therapy**

The venodilatation that occurs produces a relative hypovolemia in patients with severe sepsis. Administration of fluids, usually crystalloids such as isotonic sodium chloride solution or lactated Ringer’s solution, is the standard first-line treatment of severe sepsis. If started early, before the sepsis is too widespread, fluid therapy may help. In a recent study examining early resuscitation to a defined goal, when sufficient fluids or inotropic agents were delivered within the first 6 hours after diagnosis in patients with severe sepsis, mortality...
was significantly reduced. Measurement of resuscitation goals in the control group used the standard end points of central venous pressure, mean arterial pressure, and urine output. In the experimental group, a new triple-lumen catheter that measures mixed venous oxygen saturation (ScvO\textsubscript{2}) was used along with standard end points of resuscitation. The percentage reduction in mortality achieved in this study can be converted into a number needed to treat (NNT), a clinically usable statistic that makes the data more relevant to bedside practitioners. In this study, the NNT to save 1 life was 8 (NNT refers to how many patients must be given the treatment in order to save 1 additional life). However, as severe sepsis worsens, the benefits of fluid therapy are reduced, mainly because fluid therapy alone cannot address the cellular problems seen in severe sepsis. In addition, the capillaries have an increased permeability, allowing fluid to leak from them.

For example, consider a person with a low central venous pressure or wedge pressure (pulmonary artery occlusion pressure). A fluid bolus has very little effect on central venous or wedge pressure. The fluid is most likely leaking from the capillaries into the interstitial space or, because of widespread endothelial damage, vasodilatation and capillary permeability are so great that pressure simply cannot be developed in the system.

**Vasopressor Therapy**

Like fluid therapy, vasopressors are used to treat the disruption in the endothelial wall. The vasodilatation that takes place is treated with arterial constrictors. The hope is that the increased constriction will lead to improved perfusion. Unfortunately, vasopressors may or may not actually help improve tissue perfusion because the vasoconstriction does little to improve the obstruction at the capillary level or the cell’s inability to use oxygen and may actually reduce perfusion in some tissues. Some patients do not respond to vasopressor therapy. This lack of response may be a symptom of the relative adrenal insufficiency that is often seen in patients with...
Preventing infection will not cure sepsis but it is an important component in reducing complications and helping reduce mortality risk

SUPPORTIVE THERAPY

A number of evidence-based supportive therapies can help minimize or prevent worsening of the injury created by the pathophysiological sequelae of severe sepsis. These include lung protective strategies, management of the hyperglycemia seen in critical illness, and preventing the development of additional infections, specifically ventilator-associated pneumonia (VAP).

Mechanical Ventilation

Patients with sepsis are at a greater risk for the development of acute lung injury and acute respiratory distress syndrome (ARDS). In 2000, the ARDS Network published a landmark study demonstrating the benefits of lung protective strategies for patients with acute lung injury and ARDS. When managed by using mechanical ventilation with low tidal volume such as 6 mL/kg (ideal body weight) and maintenance of plateau pressures at 30 cm H2O or less, patients had an absolute reduction in risk of mortality of 9% or an NNT of 10 in order to save 1 life.

Tight Glycemic Control

Management of hyperglycemia in critically ill patients also affects mortality. In a study of 1500 surgical ICU patients in a 12-month period, when blood sugar level was kept within a tight range of 80 to 110 mg/dL, mortality was significantly reduced by 3.4% with an NNT of 29 in order to save 1 life. The effect was more pronounced in patients with sepsis. Recently, the same data were evaluated to determine where the benefit might originate. It appears that the tight control of the blood glucose level rather than the amount of insulin administered causes the beneficial effect. Compared with normoglycemia of 80 to 110 mg/dL, blood glucose levels from 110 to 150 mg/dL were associated with a worse outcome.

Prevention of Infection

While in the ICU, critically ill patients are vulnerable to additional infections that can affect morbidity and mortality. The role of critical care nurses in preventing infection is key. One of the greatest infection risks that critically ill patients face is the development of VAP. A number of strategies (eg, aggressive mobility plan/continuous lateral rotation therapy, reduction of ventilator circuit changes, semirecumbent positioning of patients, oral care, early enteral feeding) could reduce the risk of VAP and are easily implemented by bedside nurses.

Simply maintaining the head of the bed at 30° elevation or greater can significantly reduce the development of VAP. In a prospective study of 86 patients receiving mechanical ventilation, microbiologically confirmed VAP developed in 23% of the supine patients versus 5% of semirecumbent patients. Supine position and enteral nutrition were 2 independent risk factors for VAP and, when present, were associated with a 50% VAP rate.

A growing body of literature supports the influence of oral care on reducing oropharyngeal colonization and therefore the risk of nosocomial pneumonia. The mouth is colonized within 24 hours of intubation. Evidence suggests a direct link between pathogens in the sputum and matching pathogens in the oral cavity and on suctioning equipment. We also know that dental plaque is a reservoir for pathogens that can contribute to VAP. In a recent study by Fourrier et al, 57 medical ICU patients were assessed for 3 months for dental plaque. A correlation was found between colonization of dental plaque and the presence of the same organism in the respirato-
Xigris is not the end of development in...treatment of severe sepsis. It is, however, a significant advancement in clinicians’ ability to alter the course of the disease and signals hope for the future of treatment of severe sepsis.

Protein C is an endogenous blood protein. When converted to its active form by thrombin, it exhibits multiple mechanisms of action, resulting in a return of homeostasis and improved organ function. Protein C levels are depleted in severe sepsis. The theory developed that it was, in fact, activated protein C that was essential for the course of severe sepsis to be diverted. Xigris is a recombinant form of human activated protein C. Endogenous activated protein C has at least 3 known actions. One of the key actions is inhibition of thrombin generation, thus preventing further clot formation. This antithrombotic property is a result of direct inactivation of factors Va and VIIIa of the clotting cascade. Endogenous activated protein C also inhibits the release of plasminogen activator inhibitor-1 and, by blocking thrombin formation, impairs the release of thrombin activatable fibrinolysis inhibitor, thus allowing the body's fibrinolytic system to break down microvascular thrombi (Figure 7). By interfering with inflammatory mediators such as tumor necrosis factor, the inflammatory response is modified. Fewer neutrophils will congregate in an area, thus reducing the inflammatory damage and response, particularly of the endothelium. By administering Xigris, we are restoring a naturally occurring protective protein that allows a return toward homeostasis in the microvasculature and recovery of balance in some of the derangements due to severe sepsis.

Issues in the Use of Xigris

Several factors may influence the decision to use Xigris:
1. recognition of severe sepsis
2. bleeding risk
3. cost
4. efficacy and safety

Recognition of Severe Sepsis
The ability to determine which patients may be can-
didates for treatment with Xigris is a critical first step. Typical guidelines include the following parameters. The patient must

1. have a known or suspected infection,
2. have 2 or more signs of systemic inflammatory response syndrome (SIRS),
3. have at least 1 failing organ, and
4. be at a high risk of death (eg, as determined by using APACHE II or another system for scoring severity of disease, presence of multiple organ dysfunctions).

Strategies such as the APEX mnemonic may make it even easier to determine which patients would benefit from treatment with Xigris. If a patient is receiving an Antibiotic and a vasoPressor, consider Evaluating for Xigris therapy; that is, if the patient has an infection and a failing organ (eg, in the cardiovascular system), the patient may be an appropriate candidate for Xigris therapy. Additionally, the vasopressor requirement serves as a clinical marker for patients at a high risk of death. Recognizing severe sepsis is essential, and nurses can play the leading role in doing so because they are present at the bedside.

**Bleeding Risk**

Xigris has only a few contraindications, and they center on risk of bleeding (Table 4). The risk of bleeding with Xigris therapy is a result of impaired thrombin formation and increased fibrinolytic activity. Although elevated, the risk of serious bleeding was only slightly higher in patients treated with Xigris (3.5%) than in patients treated with placebo (2%). Additional warnings are associated with the use of this drug (Table 5), but the risk of bleeding may be small in comparison with the risk of death from severe sepsis and the greater likelihood of survival with Xigris therapy. Physicians must do an appropriate risk-benefit analysis when deciding to administer any treatment, and this requirement is no different with Xigris.

Approximately 80% of the drug’s effects will be cleared within 30 minutes, and its activity is reduced substantially in as little as 15 minutes. If a procedure is planned that is invasive or associated with a risk of bleeding (eg, surgery), the drug infusion should be interrupted 2 hours before the procedure. Once adequate hemostasis has been achieved, further administration of the drug may be reconsidered 12 hours after the procedure (for major invasive procedures) or sooner in the case of uncomplicated, less invasive procedures. If serious or clinically important bleeding occurs, the infusion of Xigris should be immediately discontinued.

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**Figure 7** Role of activated protein C for patients with severe sepsis. Copyright ©2002, Eli Lilly and Company. All rights reserved.

**Table 4** Contraindications to Xigris

<table>
<thead>
<tr>
<th>Contraindications to Xigris</th>
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<tbody>
<tr>
<td>• Active internal bleeding</td>
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<tr>
<td>• Recent (within past 3 months) hemorrhagic stroke</td>
</tr>
<tr>
<td>• Recent (within past 2 months) intracranial or intraspinal surgery or severe head trauma</td>
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<tr>
<td>• Trauma with increased risk of life-threatening bleeding</td>
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<tr>
<td>• Presence of an epidural catheter</td>
</tr>
<tr>
<td>• Intracranial neoplasm or mass or evidence of cerebral herniation</td>
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</tbody>
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**Table 5** Partial list of warnings for Xigris use (risk/benefit issues)

<table>
<thead>
<tr>
<th>Warnings for Xigris use (risk/benefit issues)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Concurrent therapeutic heparin</td>
</tr>
<tr>
<td>• Platelet level &lt; 30 x 10^9/L</td>
</tr>
<tr>
<td>• International normalized ratio &gt; 3.0</td>
</tr>
<tr>
<td>• Recent (within past 6 months) gastrointestinal bleeding</td>
</tr>
<tr>
<td>• Recent administration (within past 3 days) of thrombolytic therapy</td>
</tr>
<tr>
<td>• Recent administration (within past 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors</td>
</tr>
</tbody>
</table>

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Full list of warnings can be found in Xigris package insert.
Cost

Currently, Xigris costs about $6800 for a 96-hour infusion in a 70-kg patient. This cost has caused many hospitals and pharmacy departments to adopt strict guidelines for the use of this treatment. This response is surprising for 2 reasons. First, Xigris is the only drug that has been shown to improve the likelihood of survival of patients with severe sepsis. It is ethically inappropriate to limit the use of this drug because of cost concerns alone, if the patient’s clinical condition dictates that he or she should receive the therapy. When both survivors and nonsurvivors were included, neither hospital length of stay nor hospital costs were higher in the Xigris group than in the placebo group. In addition, Xigris is no more costly than many lifesaving treatments currently in use (Figure 8).

Costs for treatment of severe sepsis can be addressed in many ways other than limiting the pharmacy costs of a lifesaving treatment. Hospitals can reduce costs by implementing evidenced-based protocols. Studies have shown that nurse-directed programs intended to improve communication at the end of life, sedation protocols, and weaning protocols driven by nurses or respiratory therapists, or physicians can save hundreds of thousands, if not millions of dollars, in each ICU. Hospitals often approach costs in a narrow manner. Pharmacy departments are perhaps unfairly expected to control costs of novel new therapies, when it makes more sense to look at hospital costs from a multidisciplinary perspective. For example, more rapid resolution of organ dysfunction could reduce time receiving vasopressors, mechanical ventilation, or renal replacement therapy, all treatments that result in substantial costs. Unfortunately, the cost-containment approach in some institutions may effectively block lifesaving treatments from patients as a way of saving money.

If severe sepsis has been diagnosed and documented in sufficient numbers in the 2-year period beginning in October 2002, Medicare is considering developing a diagnosis-related group for severe sepsis. Xigris was the first technology approved for reimbursement under the Benefits Improvement and Protection Act of 2000. In terms of current Medicare reimbursement, a hospital can be compensated for up to 50% of the cost to acquire this drug for patients exceeding the payment rate for that diagnosis-related group (maximum reimbursement $3400 per patient).

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**Figure 8** Cost-effectiveness of various interventions in critically ill patients.

CABG indicates coronary artery bypass graft; CPR, cardiopulmonary resuscitation; QALY, quality-adjusted life years; rhEPO, recombinant erythropoietin; tPA, tissue plasminogen activator.

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**Figure 9** Number needed to treat with severe sepsis. When limited to high-risk patients (eg, those with a score ≥25 on the Acute Physiology and Chronic Health Evaluation), the number needed to treat is 8. Thus, 100 patients treated with Xigris results in 13 additional survivors.

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**Efficacy**

Xigris improves survival in many patients with severe sepsis. In the PROWESS study, Xigris treatment was associated with a 6% absolute reduction in mortality. In patients at a high risk of death (eg, patients with an APACHE II score ≥25), mortality was reduced by 13%, with a relative mortality reduction of 29% and an NNT of 8 to save 1 life (Figure 9). This impact is better than has been seen in other accepted clinical trials. Xigris is not the complete solution to the treatment of severe sepsis, but it is the only known effective treatment and is our only real option at this time.

**CASE STUDY 1**

**Part 1 – Does this patient have severe sepsis?**

A 40-year-old man has a work-related injury of his foot, starting with a laceration near the ankle. He treated the injury himself but came to the emergency department with pain and redness in his lower leg. In the emergency department, he had a sudden change in level of consciousness. His admitting vital signs and initial clinical data were as follows:

- **Blood pressure**: 84/62 mm Hg
- **White blood cell count**: $13.1 \times 10^9/L$
- **Heart rate**: 118/min
- **Platelets**: $120 \times 10^9/L$
- **Respiratory rate**: 31/min
- **FIO$_2$ (high-humidity face mask)**: 0.50
- **Body temperature**: 39.2°C
- **SpO$_2$**: 0.91

He was treated with norepinephrine at 10 mg and was given a 500-mL fluid bolus.

Does this patient fit the severe sepsis criteria?

- a. Yes. He meets the first criterion of having an infection.
- b. He meets the SIRS criteria because the body temperature, heart rate, white blood cell count, and respiratory rate are elevated.
- c. He has organ dysfunction, with both the cardiovascular and pulmonary systems affected. Because of this, he is also at an increased risk of death.

Using the APEX model—patient required antibiotics (A), vasopressor (P), so evaluate (E), and treat with Xigris (X)—made it quicker and easier for the clinician to recognize severe sepsis.

**Part 2 – Should this patient receive Xigris?**

Yes, based on the criteria for infection, signs of SIRS, and organ dysfunction.

*Staphylococcus aureus* was cultured from the leg. Xigris was started at 24 µg/kg per hour and was stopped 2 hours before surgery. A fasciotomy was performed from the ankle to the knee, with debridement of the infected area. Twelve hours after surgery, the patient had no sign of bleeding, Xigris was restarted and infused for an additional 12 hours before being discontinued because of bleeding from the surgical site.

What is the risk of bleeding for this patient?

Although bleeding is a risk in this patient, the risk of death from severe sepsis is much higher. Xigris is 8 times more likely to save an additional life than to cause an additional serious bleeding event.

Cumulative safety data have been collected on nearly 3000 patients in compassionate use trials and in additional clinical trials. The most serious bleeding events are associated with 3 things, namely, an invasive procedure, a platelet count of less than $30 \times 10^9/L$, and meningitis. If these risk factors are not present, the risk of serious bleeding is even further reduced.

**Part 3**

The patient showed no improvement postoperatively and within 3 days renal and hepatic dysfunction developed. He died on postoperative day 7. The lesson from this case is that the risk of bleeding was viewed as more serious than the risk of death due to severe sepsis. The risk of death from sepsis should always be weighed against the risk of death from bleeding. More often than not, the risk of death from sepsis is higher.
CASE STUDY 2

Part 1 – Does this patient have severe sepsis?

A 72-year-old man is admitted to the ICU with multilobar pneumonia (community-acquired pneumonia). He lives at home with his wife and is self-sufficient. He retired about 5 years ago and is active, both physically and socially. His wife tells you he is “hardly ever sick” but has been feeling “bad” with little energy for about a week. She is worried that he may have lung cancer since he used to smoke (he quit 25 years ago).

His admission clinical data were as follows:

- Blood pressure: 84/62 mm Hg (normally 132/84 mm Hg)
- FIO2: 0.70
- Heart rate: 118/min
- Positive end-expiratory pressure: +10 cm H2O
- Respiratory rate: 32/min (before intubation)
- Assisted mandatory ventilation: 10/15
- Body temperature: 39.2°C
- PaO2: 68 mm Hg
- White blood cell count: 21 × 10^9/L (bands 3 × 10^9/L)
- SpO2: 0.92
- PacO2: 34 mm Hg
- pH: 7.31
- Bicarbonate: 19 mmol/L

He was given the following medications: dopamine, 8 µg/kg per minute; 150 mL/h of isotonic sodium chloride solution; and piperacillin.

Does this patient meet the criteria for severe sepsis?

- a. Yes. He meets the first criterion of an infection with a community-acquired pneumonia.
- b. He meets all 4 SIRS criteria because his body temperature, heart rate, white blood cell count, and respiratory rate are elevated.
- c. He has multiple organ dysfunctions, with both the cardiovascular and pulmonary systems affected, so he is most likely at a high risk of death.

Part 2 – Should this patient receive Xigris?

Yes. He has a symptomatic response to an infection. Antibiotics will help control the source of the infection, but they will not address the severe sepsis that has resulted from the infection. Because this patient is receiving a vasopressor, the indication for high risk of death is met. Community-acquired pneumonia responds effectively to administration of Xigris, reducing the absolute risk of death by 17%, which translates to an NNT of 6. In addition, this patient has no history of physical limitation or quality of life issues that would make the use of this drug questionable from a cost perspective.

Part 3

The patient received Xigris on day 2. By day 3, he was no longer receiving vasopressor therapy, and he was extubated on day 5. He was discharged from the ICU on day 7 and to home from the medical ward on day 9. The lesson from this case is that appropriate use of Xigris most likely helped this patient recover. He showed a typical response of a shorter duration of use of vasopressors and time receiving mechanical ventilation.

SUMMARY

For the first time in medical history, a drug has been shown to reduce the mortality associated with sepsis, the leading cause of death in many ICUs. Optimal use by appropriate selection of patients and early recognition of sepsis could save thousands of lives. Nurses play a major role in recognizing severe sepsis. By using the concepts introduced here, nurses can play a direct role in saving the lives of patients with sepsis.

References


CE Test Instructions

To receive CE credit for this test (ID C035S), mark your answers on the form below, complete the enrollment information, and submit it with the $14 processing fee (payable in US funds) to the American Association of Critical-Care Nurses (AACN). Answer forms must be postmarked by October 1, 2005. Within 3 to 4 weeks of AACN receiving your test form, you will receive an AACN CE certificate.

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CE Test Form

Severe Sepsis Management: Are We Doing Enough?

Objectives:
1. To identify the pathophysiologic responses that occur in sepsis
2. To differentiate the clinical signs and symptoms of sepsis and organ system dysfunction
3. To discuss the essential components of treatment of severe sepsis
4. To explain the criteria for use of drotrecogin alfa (activated) in severe sepsis

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

Program evaluation

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

The level of difficulty of this test was:
 Easy   Medium   Difficult

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CE Test Questions
Severe Sepsis Management: Are We Doing Enough?

1. The pathophysiology of severe sepsis is associated with all except which of the following responses?
   a. Excess coagulation
   b. Suppression of the immune response
   c. Impaired fibrinolysis
   d. Exaggerated inflammation

2. Which of the following factors acts to suppress fibrinolysis in severe sepsis?
   a. Plasminogen
   b. Thrombin activatable fibrinolysis inhibitor
   c. Tissue factor
   d. E-selectin

3. Oxygen radicals are oxygen molecules that have how many electrons?
   a. 4
   b. 6
   c. 8
   d. 10

4. Which of the following threats to tissue oxygenation is associated with an elevated S\text{\textsubscript{VO_{2}}} level?
   a. Left ventricular dysfunction
   b. Hypovolemia
   c. Sepsis
   d. Adult respiratory distress syndrome

5. Which of the following is not considered a sign of systemic inflammatory response syndrome?
   a. Elevated temperature
   b. Tachypnea
   c. Hypotension
   d. Increased white blood cell count

6. Pulmonary dysfunction is present if a patient has an oxygen saturation <95% and requires what fraction of inspired oxygen?
   a. 0.30
   b. 0.40
   c. 0.50
   d. 0.60

7. What is the mortality rate associated with failure of 2 organ systems in severe sepsis?
   a. 10%
   b. 20%
   c. 30%
   d. 40%

8. Which of the following organ systems is among the most common to fail in severe sepsis?
   a. Renal
   b. Hematologic
   c. Hepatic
   d. Cardiovascular

9. Criteria for the use of drotrecogin alfa (activated) include all except which of the following?
   a. Suspected infection
   b. Having at least 3 or more failing organs
   c. Meeting 2 or more criteria for systemic inflammatory response syndrome
   d. High risk of death

10. Which of the following aspects of treatment during critical illness may indicate the need for drotrecogin alfa (activated) therapy?
    a. Blood transfusion
    b. Vasopressor therapy
    c. Insertion of a central catheter
    d. Blood cultures

11. Which of the following is a contraindication for the use of drotrecogin alfa (activated)?
    a. History of myocardial infarction
    b. Protein C deficiency
    c. Prior use of drotrecogin alfa (activated) therapy
    d. Active bleeding

12. Which of the following is not considered a barrier for the use of drotrecogin alfa (activated)?
    a. Failure to diagnose high risk severe sepsis
    b. Lack of understanding of the efficacy of the drug
    c. The cost of the drug
    d. Failure of the patient to meet the criteria for use of the drug
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Crit Care Nurse 2003;23 S2-S15
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