ROLE OF ACTIVATED PROTEIN C IN THE PATHOPHYSIOLOGY OF SEVERE SEPSIS

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Sepsis is a complex syndrome that can lead to multiple organ failure and death. Severe sepsis has been associated with mortality rates ranging from 28% to 50% and is the most common cause of death in the noncardiac intensive care unit. Despite advances in both antibiotic therapy and supportive care, the mortality rate due to severe sepsis has remained fundamentally unchanged in the past several decades. With increased understanding of the pathophysiology of sepsis, particularly the intricate interplay between activation of coagulation and inflammation, novel therapeutic agents that may improve clinical outcomes are being researched and developed. The epidemiology, pathophysiology, and treatment of severe sepsis are reviewed. Also discussed are the recently published results from a multicenter, randomized, placebo-controlled phase 3 clinical trial of drotrecogin alfa (activated), a recombinant form of human activated protein C, in patients with severe sepsis. The nursing implications of this new approved therapy are discussed. (American Journal of Critical Care. 2003;12:518-526)

Despite advances in critical care during the past several decades, sepsis continues to be associated with high mortality and morbidity.1 Sepsis affects persons of all age groups, including healthy and chronically ill persons. Despite improvements in diagnosis and intensive therapy, sepsis remains an increasing problem.2 Factors contributing to the increasing incidence of sepsis include an aging population; advances in invasive procedures, increases in the number of patients who are immunocompromised because of intense therapies for cancer, organ transplantation, autoimmune diseases, and, perhaps, improved diagnostic awareness. Other contributing factors include increases in nosocomial infections and antimicrobial resistance to antibiotic therapy.3 Sepsis currently accounts for the use of a large part of healthcare resources1 and, as the incidence increases, will be an escalating burden on healthcare resources.

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Pathophysiology of Sepsis and Severe Sepsis

Sepsis is not a disease but a syndrome. It is characterized by a systemic inflammatory response to infection whether the infection is systemic (eg, gram-negative sepsis, meningococcemia) or localized (eg, abscess). This response, termed the systemic inflammatory response syndrome (SIRS), is not specific for sepsis; it may occur as a result of other processes such as trauma, burns, and pancreatitis. Severe sepsis is defined as sepsis associated with evidence of one or more acute organ dysfunctions. Sepsis causes disruption of homeostasis through a currently uncontrollable cascade of excessive inflammation and coagulation with impaired fibrinolysis that contributes to an inflammatory response, microvascular hypoperfusion, organ dysfunction, and increased mortality. The magnitude of disruption in homeostasis is influenced by the virulence of the causative pathogens and the host’s response to the infection.

It has been known for at least 30 years that the magnitude of activation of coagulation in patients with sepsis is related to the patients’ shock status. The activation of coagulation is independent of the infectious microorganism; it occurs with infections caused by gram-positive and gram-negative bacteria, viruses, fungi, and parasites. In addition to coagulation abnormalities, abnormalities in fibrinolysis also occur in patients with sepsis. The evolving understanding of the body’s response at the molecular level continues to reveal common pathways between infection, inflammation, and hemostasis.

During sepsis, the normal balance between clotting and clot breakdown “tips” toward clotting.

Although inflammation is the normal bodily response to infection, in severe sepsis, regulation of this response is perturbed, leading to an exaggerated response. The clinical manifestations of SIRS include thermodysregulation, causing fever or hypothermia; tachycardia; tachypnea; and elevated or abnormally decreased white blood cell count with or without a shift to the left. Inflammation may occur in response to bacteria, viruses, fungi, or parasites.

In response to infectious pathogens or their byproducts, monocytes and macrophages generate and release proinflammatory cytokines. The role of these cytokines is to assist in the body’s defense by attracting activated neutrophils to the site of infection. However, cytokines can also cause widespread activation of coagulation and suppression of fibrinolysis. They are also involved in producing damage to the endothelium that may result in capillary leak and other deleterious actions.

Normally, the body maintains a homeostatic balance between coagulation and fibrinolysis. In sepsis, this equilibrium is altered, and the balance shifts toward increased coagulation over fibrinolysis. Coagulation via the extrinsic pathway is activated by stimulating the cell-surface expression of tissue factor and activated factor VIIa on monocytes and the endothelium, leading to activation of factor X, generation of thrombin (factor IIa), and deposition of fibrin (clot). This chain of events has been detected in animal models of endotoxemia (endotoxin is released from the cell walls of gram-negative bacteria). In a study in rats by Asaka et al, microthrombi developed in the hepatic circulation within 5 minutes of injection of endotoxin. With continued exposure to endotoxin, multiple fibrin clots developed, resulting in focal areas of hypoperfusion, tissue necrosis, and development of multiple organ dysfunction.

Under normal circumstances, the body’s endogenous fibrinolytic and anticoagulant systems are activated in an attempt to reverse excessive activation of coagulation. These compensatory mechanisms are suppressed in sepsis and cannot adequately counteract fibrin deposition. Within the fibrinolytic system, plasmin is generated from plasminogen by tissue plasminogen activator, which upon activation lyses fibrin clots. Inflammatory cytokines and thrombin can impair this system by stimulating platelets and the endothelium to release plasminogen activator inhibitor-1, the principal inhibitor of the fibrinolytic system, and limit the availability of tissue plasminogen activator. Thrombin can also stimulate inflammatory pathways and further reduce the body’s fibrinolytic capabilities by activating thrombin-activatable fibrinolysis inhibitor to suppress the activity of plasmin.

Regulation of thrombin formation involves 3 anticoagulant systems: protein C, antithrombin, and tissue factor pathway inhibitor. Protein C, an inactive precursor of activated protein C, is converted to activated protein C by thrombin in complex with thrombomodulin, an endothelial cell-surface receptor. Activated protein C inactivates 2 key cofactors responsible for the generation of thrombin from pro-thrombin: factors Va and VIIIa. Activated protein C thereby inhibits thrombosis and promotes fibrinolysis. In vitro data indicate that activated protein C exerts an anti-inflammatory effect by inhibiting the produc-
tion of inflammatory cytokines by monocytes and limiting the rolling of monocytes and neutrophils on injured endothelium by binding to cell adhesion molecules called selectins.\textsuperscript{5} The conversion of protein C to activated protein C may be less than optimum during severe sepsis. Levels of thrombomodulin on the surfaces of endothelial cells may be decreased as a result of endothelial injury, thus further limiting the conversion of protein C to activated protein C.\textsuperscript{11,12}

Another important inhibitor of thrombin is antithrombin III. As a result of ongoing coagulation, plasma levels of antithrombin III are reduced, often severely. Levels of this inhibitor can also be reduced because of degradation by elastase released from activated neutrophils or impaired synthesis of antithrombin III.\textsuperscript{13}

The complex consisting of tissue factor, factor VIIa, and factor Xa, which triggers coagulation and thus causes microthrombi and organ dysfunction in sepsis, is inhibited by tissue factor pathway inhibitor. The role of abnormal levels and the function of tissue factor pathway inhibitor in sepsis are being investigated. Regulation of the activity of tissue factor is abnormal in patients with disseminated intravascular coagulation.\textsuperscript{5}

Clearly, sepsis can no longer be viewed as merely an infectious process. The finding that sepsis is more than a response to infection helps explain why current state-of-the-art care and antimicrobial agents do not improve survival in patients with severe sepsis. We now understand that sepsis involves a multitude of interrelated processes. The pathways in inflammation and coagulation have been explored extensively in the past decade. The role of endogenous activated protein C in inflammation and coagulation suggests that this protein is an important regulator of coagulation, fibrinolysis, and inflammation associated with severe sepsis. We are at the beginning of what appears to be a new era of clinical treatment and research related to this complex syndrome.

**Diagnosis**

Diagnosis of sepsis begins with early recognition that the patient may have this abnormality. Confusion exists among practitioners about the various definitions associated with sepsis. The onset of SIRS is often the first indicator of sepsis.\textsuperscript{14} In a clinical trial\textsuperscript{15} of patients with SIRS, entry criteria were 3 or more of the following: body temperature greater than 38°C or less than 36°C, heart rate greater than 90/min, respirations greater than 20/min or PacO\textsubscript{2} less than 32 mm Hg or the use of mechanical ventilation, or white blood cell count greater than 12.0 x 10\textsuperscript{9}/L or less than 4.0 x 10\textsuperscript{9}/L or more than 10% immature neutrophils (bands). However, SIRS can also be caused by noninfectious conditions such as burns, pancreatitis, or trauma.

Sepsis is the specific instance of SIRS caused by infection. Severe sepsis is sepsis with associated acute organ dysfunction. Common criteria for organ dysfunction are systolic blood pressure less than 90 mm Hg for at least 1 hour despite adequate fluid resuscitation or adequate intravascular volume status and/or the need for vasopressors; urine output less than 0.5 mL/kg per hour for 1 hour despite adequate fluid resuscitation; evidence of acute pulmonary dysfunction, defined as a ratio of PaO\textsubscript{2} to fraction of inspired oxygen of 250 or less; platelet count less than 80.0 x 10\textsuperscript{9}/L or a 50% decrease in the highest value recorded during the past 3 days; and unexplained metabolic acidosis, defined as pH 7.30 or lower or a base deficit of 5.0 mmol/L or greater in the presence of an elevated lactate level greater than 1.5 times the upper limit of normal.

In summary, patients with known or suspected infection should be evaluated for the source of infection and for acute organ dysfunction indicating severe sepsis. Early recognition and treatment can often prevent progression to a life-threatening episode.

**Standard Therapy**

Primary treatment for sepsis is directed at the cause, and then symptom-specific therapy is used. Treatment may require surgical interventions, medical interventions, or a combination of therapies. Cases that require a surgical approach for control of the primary source of sepsis may include perforated viscus, ruptured esophagus or diaphragm, instances of severe burns or abscesses, and gangrene. All patients with sepsis require immediate therapy with appropriate antimicrobial agents. In cases in which the infecting organism is unknown, broad antimicrobial coverage against gram-negative, gram-positive, and anaerobic organisms is generally instituted. In patients with immunosuppression, treatment against fungal organisms or other opportunistic organisms is often required. Once the infecting organism or organisms have been identified, therapy is directed specifically. Because of the prevalence of nosocomial infections, institutional patterns of common pathogens and antimicrobial resistance play an important role in the choice of empirical therapy. However, treating and eradicating the infection with appropriate antimicrobial agents does not necessarily arrest the progression of sepsis because of the cascades of inflammation and coagulation that occur in this abnormality.

Patients with severe sepsis are prone to shock from stimulation of the inflammatory cascade with
subsequent decreased systemic vascular resistance and capillary leak. As a result, tissue perfusion and oxygen delivery are impaired, leading to organ dysfunction. Adequate fluid replacement is the initial step in restoring cardiac index and systemic oxygen delivery to injured tissues. Depending on the patient and the situation, adequate fluid volume may be defined as a pulmonary capillary wedge pressure of at least 12 to 15 mm Hg or a central venous pressure of at least 8 mm Hg. A minimum urinary output of at least 0.5 mL/kg per hour (ie, urine volume in milliliters to equal or exceed the patient’s weight in kilograms every 2 hours) is considered adequate by most physicians. Restoration of blood pressure and return of heart rate to the normal range are additional indicators of adequate intravascular volume. Fluid volume needs are variable among patients with sepsis who are in shock. When blood pressure cannot be sufficiently improved with fluids alone, the addition of vasopressor therapy may be necessary to improve hemodynamic performance and preserve organ function.

The purpose of the treatments described is to control the infection and support the patient physiologically. Although these treatments are the standard of care for patients with sepsis, mortality is still 28% to 50%. Physicians’ current perspective is that over time the body can repair itself if supported adequately. However, none of these supportive therapies controls the rampant thrombotic and inflammatory processes. Controlling the level of thrombosis and inflammation is thought to be a primary determinant of who survives.

### Sepsis Research

In the past decade, approximately 60 randomized, placebo-controlled clinical trials, most with antiendotoxin or antiendotoxin agents, were conducted in more than 15,000 patients with sepsis. None of these anti-inflammatory agents have been approved by the Food and Drug Administration as therapy for severe sepsis. The results of multiple trials suggest that interventions targeted to isolated components of the inflammatory response, among all the host responses to infection, may be insufficient. As discussed earlier, these host responses overlap and have several mediators in common that when activated, trigger both the inflammatory and the coagulation cascades. However, endogenous activated protein C plays a vital role in each of the 3 components in sepsis: inflammation, coagulation, and fibrinolysis (see Figure).

As an anti-inflammatory, activated protein C inhibits production of proinflammatory cytokines by monocytes and limits the rolling of monocytes and neutrophils on the injured endothelium via selectins. As an anticoagulant, it inactivates factors Va and VIIIa, thus limiting the generation of thrombin, which also has an indirect anti-inflammatory effect. As a profibrinolytic, it inactivates plasminogen activator inhibitor-I and decreases activation of thrombin-activatable fibrinolysis inhibitor. Activated protein C also limits the adherence of neutrophils to vascular endothelium.

In an experimental study of gram-negative septicemia in baboons, administration of activated protein C along with a 100% lethal dose of Escherichia coli (ie, a source of endotoxin) prevented lethality in all the animals tested. When animals were pretreated with an antibody specific for activated protein C, injection of a sublethal dose of the organisms became 100% lethal. These results illustrate the pivotal role of endogenous activated protein C in the pathophysiology of severe sepsis. These properties of activated protein C have led to the development of drotrecogin alfa (activated), a recombinant form of human activated protein C.

In July 1998, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis
The (PROWESS) study was initiated. Patients were randomized to receive either drotrecogin alfa (activated) at 24 µg/kg per hour or a placebo for 96 hours of total infusion time. The primary efficacy end point was mortality due to all causes 28 days after the start of drug administration. Prospectively defined subsets for mortality analyses included groups defined according to scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II (calculated during the 24-hour period immediately preceding the start of drug administration), protein C activity, and the number of acute organ dysfunctions at baseline.

In June 2000, enrollment was suspended because the differences in mortality rates between the groups had exceeded the prospectively set stopping rules for efficacy. All-cause 28-day mortality was 30.8% in the placebo-treated group and 24.7% in the drotrecogin alfa (activated) group ($P = .005$). Statistical analyses indicated an adjusted relative risk reduction of 19.4% and an increase in odds of survival of 38.1%. The observed difference in mortality between patients given drotrecogin alfa (activated) and those given placebo was limited to patients with higher risk of death (ie, APACHE II score $\geq 25$, the third and fourth
quartile APACHE II scores). In these patients, mortality was reduced from 44% in the placebo group to 31% in the treatment group. The efficacy of drotrecogin alfa (activated) has not been established in patients with lower risk of death (eg, APACHE II score <25). In patients with APACHE II scores less than 25, mortality was 19% in both placebo and treatment groups (95% CI = 0.75-1.30).

In the PROWESS trial, serious bleeding occurred more often in patients receiving drotrecogin alfa (activated) than in patients receiving placebo (3.5% and 2.0%, respectively; \( P = .06 \)). The difference in serious bleeding between the 2 groups occurred primarily during the 96-hour infusion period.

Drotrecogin alfa (activated) is the first medication that can decrease 28-day all-cause mortality in adults with severe sepsis who are at a high risk of death and has an acceptable safety profile within the context of the PROWESS trial. The results indicate that 1 in every 5 patients who would have died were saved with drotrecogin alfa (activated) treatment added to the best standard of care.15

A New Therapy

Drotrecogin alfa (activated) is the generic name for the recombinant form of human activated protein C. Drotrecogin alfa (activated) is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (eg, as determined by APACHE II scores). Pharmacokinetic studies indicated no clinically significant differences in the plasma clearance of drotrecogin alfa (activated) with regard to age, sex, hepatic function, or renal function, indicating that a dose adjustment is not required on the basis of these criteria. Drug interactions with drotrecogin alfa (activated) have not been studied in patients with severe sepsis. The drug must be administered via a dedicated intravenous catheter or a dedicated lumen of a multilumen central venous catheter.

**Activated protein C therapy reduces inflammation and clotting and increases clot breakdown.**

Routine care of patients with severe sepsis includes measuring parameters of hemostasis, such as activated partial thromboplastin time (APTT), prothrombin time, or platelet count. Drotrecogin alfa (activated) has a minimal effect on the prothrombin time but can prolong the APTT. Prolongation of the APTT should not be used to assess the pharmacodynamic effect of drotrecogin alfa (activated). If routine sequential tests of hemostasis during the infusion of drotrecogin alfa (activated) indicate an uncontrolled or worsening coagulopathy that markedly increases the risk of bleeding, the benefits of continuing the infusion must be weighed against the potential increased risk of bleeding.

**Bleeding is the most common adverse effect, but a prolonged activated partial thromboplastin time alone should not cause a drug to be discontinued.**

Merely having an abnormal laboratory value does not require stopping the infusion. In clinical trials, infusions of drotrecogin alfa (activated) were not necessarily stopped in patients with severe thrombocytopenia or disseminated intravascular coagulation. Patients with abnormal coagulation profiles or disseminated intravascular coagulation received standard care for coagulopathy, including fresh-frozen plasma, packed red blood cells, and whole blood. In practice, physicians and nurses must be cognizant of the increased risk of serious bleeding (including intracranial hemorrhages) in patients with severe thrombocytopenia (platelet count <30 x 10^9/L) and must weigh this risk against the benefits of survival in these patients.

**Contraindications to Drotrecogin Alfa (Activated)**

Drotrecogin alfa (activated) increases the risk of bleeding because of its antithrombotic and profibrinolytic effects. It is contraindicated in patients with the following situations in which bleeding could be associated with a high risk of death or marked morbidity:

- active internal bleeding,
- recent (within 3 months) hemorrhagic stroke,
- recent (within 2 months) intracranial or intraspinal surgery or severe head trauma,
- trauma with an increased risk of life-threatening bleeding,
- presence of an epidural catheter, and
- intracranial neoplasm or mass lesion or evidence of cerebral herniation.

Bleeding is the most common serious adverse effect associated with drotrecogin alfa (activated) therapy. Each patient being considered for therapy...
should be carefully evaluated, and anticipated benefits should be weighed against the potential risks associated with therapy. Because drotrecogin alfa (activated) has antithrombotic effects, whenever possible invasive surgical procedures should be performed at least 12 hours before therapy with the drug is started. Because of the acute nature and often-rapid progression of sepsis, surgical or bedside procedures may be required during the 96-hour infusion. Use of drotrecogin alfa (activated) does not preclude performing emergency procedures or replacing central catheters. In order to limit the risk of bleeding, drotrecogin alfa (activated) should be discontinued for 2 hours (plasma drug levels are less than the limits of detection in most patients within 2 hours after infusion of the drug is stopped) before the start of the procedure. For uncomplicated less invasive procedures, drotrecogin alfa (activated) can be restarted immediately once adequate hemostasis has been achieved after the procedure. For major invasive procedures or surgery, it may be reconsidered 12 hours after the procedure.

Conclusion

Sepsis remains a challenging and complex disease despite advances in conventional critical care during the past 2 decades. Use of aggressive standard supportive measures may not be sufficient to control the widespread inflammatory process and disruption in homeostasis due to inflammation, fibrinolysis, and coagulation. A novel therapy, infusion of drotrecogin alfa (activated), an agent with multiple mechanisms of action (antithrombotic, profibrinolytic, and anti-inflammatory), in patients with sepsis significantly reduced morbidity and mortality in a large phase 3 clinical trial. The specific mechanisms by which drotrecogin alfa (activated) exerts its effect on survival in patients with severe sepsis are not completely understood.

As more is learned about the role of coagulation and inflammation in sepsis, other therapies may emerge. Many other clinical trials of potential treatments for acute respiratory distress syndrome and severe sepsis are under way. Some of the agents under investigation include naturetic hormones and platelet activating factor acetylhydrolase. Other areas of investigation include validation of modes of standard-of-care therapies, including fluid management, nutritional support, and use of vasopressors. Development of each new therapy will enhance the ability of physicians and nurses to augment survival in patients with severe sepsis and will expand the knowledge of this complex and deadly disease.

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REFERENCES

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CE Test Questions

Role of Activated Protein C in the Pathophysiology of Severe Sepsis

1. Which of the following statements is true regarding sepsis?
   a. Sepsis is a disease characterized by a systemic inflammatory response.
   b. The incidence of sepsis has decreased because of advances in invasive procedures available to critically ill patients.
   c. Factors contributing to the increased incidence of sepsis include an aging population and antimicrobial resistance.
   d. Approximately 250,000 cases of sepsis with acute organ dysfunction occur annually in the United States.

2. Which of the following scenarios suggests that a patient has systemic inflammatory response syndrome and could be septic?
   a. Heart rate 88 beats per minute, temperature 37.4°C, respiratory rate 26 per minute, white blood cell count 3.8 x 10^9/L
   b. Heart rate 96 beats per minute, temperature 38.4°C, respiratory rate 28 per minute, white blood cell count 14.08 x 10^9/L
   c. Heart rate 60 beats per minute, temperature 36.7°C, respiratory rate 24 per minute, white blood cell count 19.0 x 10^9/L
   d. Heart rate 100 beats per minute, temperature 38°C, respiratory rate 18 per minute, white blood cell count 9.0 x 10^9/L

3. Which of the following statements best describes severe sepsis?
   a. Sepsis associated with evidence of acute organ dysfunction
   b. Sepsis associated with intermittent hypotension
   c. Sepsis associated with excessive inflammation
   d. Sepsis associated with hypercoagulation

4. What is the normal bodily response to infection?
   a. Coagulation
   b. Hypertension
   c. Inflammation
   d. Fibrinolysis

5. What is the role of proinflammatory cytokines in relationship to infectious pathogens?
   a. Activation of fibrinolysis
   b. Attracting activated neutrophils to the site of infection
   c. Suppression of coagulation
   d. Attracting monocytes to the site of infection

6. Which of the following is true about the relationship between coagulation and fibrinolysis in patients with sepsis?
   a. Coagulation and fibrinolysis are both increased
   b. Hemostatic balance between coagulopathies and fibrinolysis shifts to an increase in fibrinolysis
   c. Coagulation and fibrinolysis are both decreased
   d. Hemostatic balance between coagulopathies and fibrinolysis shifts to an increase in coagulopathies

7. Which of the following is often the first indicator of sepsis?
   a. Onset of systemic inflammatory response syndrome
   b. Onset of hypoxia
   c. Onset of hyperthermia
   d. Identification of a gram-negative causative organism

8. Which of the following is not a criterion for acute organ dysfunction?
   a. Urine output less than 0.5 mL/kg per hour despite adequate fluid resuscitation
   b. Systolic blood pressure less than 90 mm Hg for at least 1 hour despite adequate fluid resuscitation
   c. The need for vaspressors despite adequate fluid resuscitation
   d. Unexplained metabolic alkalosis

9. Why are patients with severe sepsis prone to shock?
   a. Circulating pathogens
   b. Decreased systemic vascular resistance and capillary leak
   c. Circulation of antithrombin II
   d. Microthrombi in the hepatic circulation

10. What is the current indication for drotrecogin alfa (activated)?
    a. Adults with severe sepsis and a high risk of death
    b. Adults with sepsis and no signs of organ failure
    c. Pediatric patients with severe sepsis
    d. Adult patients with severe sepsis and active hemorrhage

11. Which of the following is a contraindication to the use of drotrecogin alfa (activated)?
    a. Severe head trauma within the past 2 months
    b. Presence of a central venous catheter
    c. Hemorrhagic stroke within 6 months
    d. A decreased activated partial thromboplastin time

12. Which of the following statements is true regarding the administration of drotrecogin alfa (activated)?
    a. Invasive procedures should be performed at least 1 hour before therapy is initiated.
    b. Bleeding is the most common serious adverse effect.
    c. Drotrecogin alfa (activated) should be infused intravenously over 48 hours.
    d. Very few drugs interact with drotrecogin alfa (activated).