

Low-Dose, Off-Label Drotrecogin Alfa (Xigris) In Severe Sepsis

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ABSTRACT

Objective: In this article, we describe a successful low-dose, off-label usage of drotrecogin alfa (Xigris), given at 18 mcg/kg per hour, in a patient with severe sepsis who had an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 26 and multiorgan failure.

Patient: A 64-year-old man was admitted to the surgical intensive-care unit of Winthrop University Hospital in Mineola, New York. After undergoing small-bowel resection secondary to obstruction, he became severely septic. Because of his high risk of death (with an APACHE II score of 26 and two organ failures), he was initially treated with drotrecogin alfa 24 mcg/kg per hour, the dose approved by the U.S. Food and Drug Administration (FDA). Within four hours, his activated partial thromboplastin time became significantly prolonged from a baseline of 27.8 to 92.9 seconds, and he had coffee-ground nasogastric tube output. In light of signs of bleeding, drotrecogin alfa was temporarily discontinued. After 26 hours without further evidence of bleeding, drotrecogin alfa was administered at a lower dose of 18 mcg/kg per hour. The manufacturer's recommendation of 96 hours of infusion therapy was completed with the lower dosing. The patient's condition improved significantly, and eventually he was discharged home.

Conclusion: This case report demonstrates an alternative use of drotrecogin alfa at a lower dose of 18 mcg/kg per hour in a severely septic patient who could not tolerate the FDA-approved dose of 24 mcg/kg per hour because of bleeding.

Key words: severe sepsis, APACHE II score, multiorgan failure, low-dose drotrecogin alfa

INTRODUCTION

Sepsis is defined as a systemic inflammatory syndrome in response to an infection. It is associated with acute organ dysfunction, which can be fatal.¹⁻³ In the U.S., sepsis affects more than 750,000 patients at an estimated annual cost of \$17 billion.^{1,3,4} Despite advances in intensive-care medicine and antimicrobial treatment, sepsis is associated with a mortality rate of 50%.⁵

The three principal components in sepsis are inflammation, coagulation, and fibrinolysis.⁴⁻⁷ Endotoxins and exotoxins are

released when an infection occurs, and they trigger a systemic response. A cascade of inflammation and activation of the coagulation system is associated with impaired fibrinolysis, which leads to alterations in microvascular circulation.^{3,6,7} Activated protein C, an endogenous protein that promotes fibrinolysis and inhibits thrombosis as well as inflammation, is one of the important modulators associated with severe sepsis.⁴⁻⁷

In 2001, the FDA approved drotrecogin alfa, a recombinant version of activated human protein C (Xigris, Eli Lilly) for the treatment of severe sepsis. Drotrecogin alfa is the first in a relatively new class of antithrombotic coagulation inhibitors for septic patients who are at high risk of dying (i.e., an APACHE II score of 25 or greater).^{4,8-10} Activated protein C inhibits factors VIIIa and Va, thereby limiting thrombin formation by promoting fibrinolysis.^{6,8,9,11}

Various dosing regimens of drotrecogin alfa in severe sepsis have been studied in a phase 2 trial. Bernard et al.¹² conducted a double-blind, randomized, placebo-controlled, multicenter, dose-ranging (sequential) clinical trial. One hundred thirty-one adults with organ failure and severe sepsis, as defined by systemic inflammatory response syndrome (SIRS) criteria, received intravenous (IV) infusions of drotrecogin alfa at 12, 18, 24, or 30 mcg/kg per hour or placebo for 48 or 96 hours. Significant dose-dependent decreases in both D-dimer and interleukin-6 (IL-6) levels at the end of the infusion were demonstrated in those receiving 18 mcg/kg per hour and 24 mcg/kg per hour.¹³

In this article, we report a case of survival in a patient with severe sepsis who was treated with low-dose drotrecogin alfa (18 mcg/kg per hour) after he experienced bleeding with the FDA-approved dose (24 mcg/kg per hour).

Case Report

A 64-year-old man was admitted to Winthrop University Hospital with a ventral hernia and a small-bowel obstruction on August 27, 2006. His medical history was significant for Crohn's disease, asthma, diverticulitis, intermittent tachycardia, and mitral valve prolapse. Previous surgeries included an open cholecystectomy and bowel resection 12 years earlier.

He arrived at the emergency department complaining of "trapped gas" with nausea, vomiting, and pain. He had no complaints of chest pain, shortness of breath, weakness, dysuria, or diarrhea. His rectal temperature was 96.6° F; heart rate, 56 beats/minute; blood pressure, 123/88 mm Hg, respiratory rate, 18 breaths/minute; and oxygen saturation, 97% in room air.

The patient underwent an exploratory laparotomy, repair of a ventral hernia, and small-bowel resection with primary anas-

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Accepted for publication July 10, 2008.

Disclosure: The authors have no commercial or financial relationships to report in regard to this article.

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tomosis. He was given 2 g of IV cefoxitin (Mefoxin, Merck) and 500 mg of IV metronidazole for surgical prophylaxis. He became hemodynamically unstable during the surgery and was intubated and transferred to surgical intensive care. Vasopressin, norepinephrine, and phenylephrine were required to maintain adequate mean arterial pressure (MAP).

On the second hospital day, the patient was returned to the operating room for a partial omentectomy and reinforcement of small-bowel anastomosis after abdominal compartment syndrome was diagnosed. Postoperatively, he exhibited signs of severe sepsis with a calculated APACHE II score of 26 and multiorgan (cardiovascular and respiratory) failure. MAP was 59 mm Hg, partial pressure of oxygen (P_{O_2}) was 51, and the arterial pH was 7.23. The patient's temperature was 101.1° F, his white blood cell count was $1.1 \times 10^3/\text{mm}^3$, and his hematocrit was stable (27.6%).

Upon evaluation of the hospital's sepsis protocol, he was considered a candidate for drotrecogin alfa. He was started on the FDA-approved dose of 24 mcg/kg per hour at 5 a.m. on hospital day 2, 12 hours after surgery. Four hours later, the patient's prothrombin time (PT) and activated partial thromboplastin time (aPTT) were prolonged significantly, 16.9 and 92.9 seconds, respectively, from a baseline value of 11 and 27.8 seconds, respectively (Figures 1 and 2). Coffee-ground nasogastric tube output was observed. Drotrecogin alfa was discontinued at this point because of signs of bleeding.

On the third hospital day, given the patient's high risk of death, the intensivist restarted drotrecogin alfa at a lower dose of 18 mcg/kg per hour after finding no evidence of continued bleeding. The patient was also given meropenem (Merrem, AstraZeneca) and vancomycin IV (Vancocin, Viro Pharma) for broad infection coverage.

On the fourth day, drotrecogin alfa was withheld for one hour so that a central line could be inserted; therapy was resumed after this procedure. The patient's hospital course was further complicated with anemia, rhabdomyolysis, metabolic acidosis, hypoadrenia, hypokalemia, thrombocytopenia, and myocardial injury.

On the fifth day, positive cultures for *Escherichia coli* in the blood and *Streptococcus pneumoniae* in the sputum were noted.

On hospital day 6, the patient underwent a tracheostomy, exploratory laparotomy, and complex abdomen wall closure with an application of banked human tissue (AlloDerm, LifeCell) graft and V.A.C. abdominal dressing (KCI Corp.). Drotrecogin alfa was placed on hold for two hours before the procedure and was restarted one hour later according to the hospital protocol.

On day 7, the patient completed the recommended 96 hours of drotrecogin alfa therapy without experiencing significant side effects. He ultimately improved clinically, and he was discharged home.

Platelets (Figure 3) and International Normalized Ratio (Figure 4) were noted every day while drotrecogin alfa therapy was being administered.

DISCUSSION

PROWESS (Recombinant Activated Human Protein C Worldwide Evaluation in Severe Sepsis) was the first successful clinical trial showing beneficial outcomes with a novel phar-

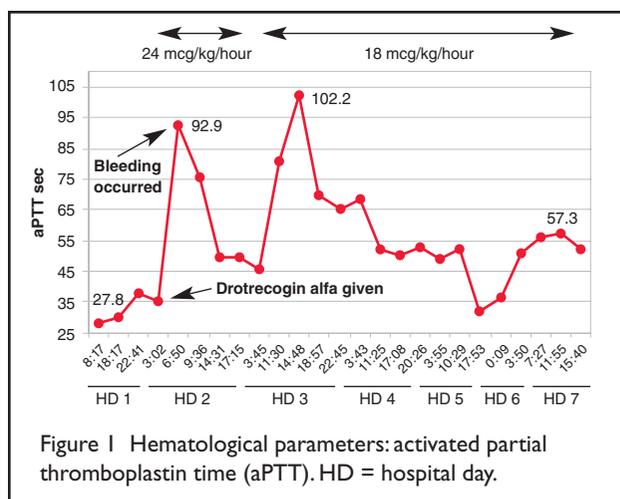


Figure 1 Hematological parameters: activated partial thromboplastin time (aPTT). HD = hospital day.

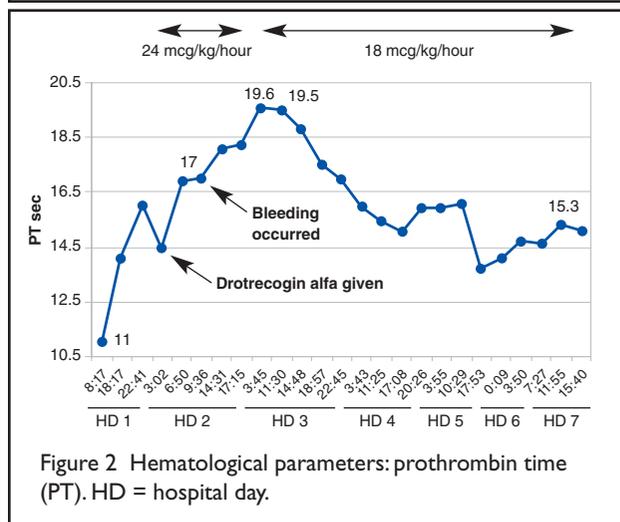


Figure 2 Hematological parameters: prothrombin time (PT). HD = hospital day.

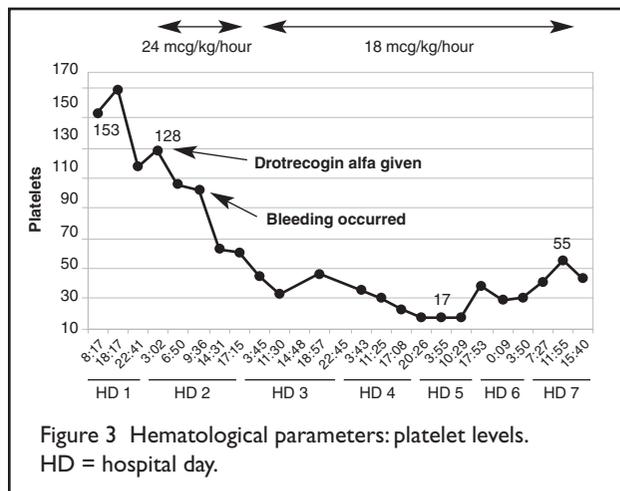
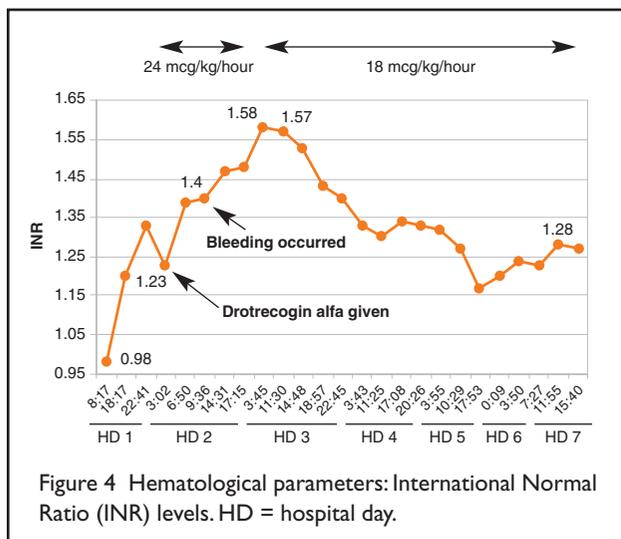


Figure 3 Hematological parameters: platelet levels. HD = hospital day.

macological therapy for severe sepsis and septic shock. Those patients with APACHE II scores of 25 or higher appear to benefit from drotrecogin alfa in terms of 28-day survival.^{4,7,8,9,10} In PROWESS, patients received an infusion of drotrecogin alfa 24 mcg/kg per hour over 96 hours or placebo within 48 hours after the onset of the first sepsis-induced organ dysfunction.

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LIMITATIONS OF THE STUDY

There were some limitations to our findings. It is possible that the patient might have survived and improved without the use of drotrecogin alfa. As clinicians, we were obligated to offer it to the patient because of his high risk of death resulting from his APACHE II score and two organ failures. Indeed, a clinical trial of low-dose drotrecogin alfa is needed in severely septic patients who cannot tolerate the FDA-approved dosing (24 mcg/kg per hour), as we observed in our case report.

CONCLUSION

Preclinical and clinical studies led the FDA to set the standard dosing for drotrecogin alfa at 24 mcg/kg per hour for patients with severe sepsis, including those with APACHE II scores above 25.^{4,9,10,12} As a result of the coffee-ground nasogastric tube output, this dose was discontinued in our patient. After the signs and symptoms of bleeding resolved, the patient received low-dose drotrecogin alfa (18 mcg/kg per hour), because of his high risk of death.

Because of this drug's potent anticoagulant property, increased PT and aPTT levels were also observed during drotrecogin alfa therapy. However, elevated aPTT levels should not be the sole reason for discontinuing drotrecogin alfa therapy, because the drug itself may interact with one-stage coagulation assays of aPTT monitoring.

On the basis of our findings in this case report, we concluded that low-dose drotrecogin alfa might be a useful alternative in severely septic patients (i.e., an APACHE II score above 25 and multiorgan failure) who cannot tolerate the FDA-approved dose of 24 mcg/kg per hour. Additional research studies and randomized controlled trials are needed to validate such use.

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Drotrecogin alfa resulted in an absolute reduction of mortality by 6%, compared with placebo (24.7% vs. 30.8%, respectively).^{4,9}

However, the ADDRESS study—Administration of Drotrecogin Alfa (Activated) in Early-Stage Severe Sepsis—did not demonstrate the drug's efficacy in patients with sepsis and a low risk of death (i.e., an APACHE II score below 25 or single-organ failure). The differences in 28-day mortality rates in the two groups were not statistically significant: 17% of 1,297 patients receiving placebo and 18.5% of 1,316 treated patients ($P = 0.34$).¹⁴

Castelli et al.¹⁵ demonstrated an association between PTT levels and drotrecogin alfa therapy. However, because drotrecogin alfa interferes with PTT assays, it is not reliable to monitor only PTT during therapy. In addition, because drotrecogin has a minimal effect on PT, PT is a more reliable laboratory value than PTT for monitoring drug therapy.

Given the anticoagulant properties of drotrecogin alfa, the major risk associated with its use is bleeding.^{3,4,9,11,16} In fact, subanalyses of the PROWESS and ADDRESS clinical trials showed a higher incidence of all-cause mortality with drotrecogin alfa than with placebo in patients with single-organ dysfunction and who had undergone surgery within the previous 30 days. The package insert lists a 3.9% incidence of serious bleeding associated with drotrecogin alfa.

A new phase 3 placebo-controlled study (PROWESS-SHOCK), scheduled to begin in 2008 in Europe and the U.S., is expected to provide additional clinical evidence for the efficacy and safety of drotrecogin alfa.¹⁷

Even though drotrecogin alfa has been studied in children with severe sepsis, the FDA halted the clinical trial because of a significant increase in intracranial hemorrhage in the treated group when compared with the placebo group.⁹

Winthrop University Hospital has a strict policy regarding use of drotrecogin alfa in sepsis. All patients must have either (1) APACHE II scores above 25 plus two or more organ failures or (2) three or more organ failures if the APACHE II score is not calculated. Patients must also be currently receiving cardiac pressors (Appendix 1).¹⁸

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Appendix 1 Winthrop University Hospital Drotrecogin alfa Protocol

Winthrop University Hospital
Hospital-Wide Critical Care Committee

Drotrecogin alfa (Xigris®) Order Form

Drotrecogin alfa is a recombinant form of human activated protein C, which exerts an antithrombotic effect by inhibiting Factors Va and VIIIa. *In vitro* data indicate that activated protein C has indirect profibrinolytic activity through its ability to inhibit plasminogen activator inhibitor-1 (PAI-1) and limiting generation of activated thrombin-activatable-fibrinolysis-inhibitor. Additionally, *in vitro* data indicate that activated protein C may exert an anti-inflammatory effect by inhibiting human tumor necrosis factor production by monocytes, by blocking leukocyte adhesion to selectins, and by limiting the thrombin-induced inflammatory responses within the microvascular endothelium. The efficacy of drotrecogin alfa was studied in an international, multi-center, randomized, double-blind, placebo-controlled trial (PROWESS) of 1,690 patients with severe sepsis. In this trial, there was an absolute mortality reduction of 13% in drotrecogin alfa-treated patients who have APACHE II score of ≥ 25 , compared to the placebo group. Similarly, absolute mortality reductions of 8% and 11% were also observed for patients with 3 or 4 organ failures, respectively. The efficacy of drotrecogin alfa has not been established in less severe patients (i.e., APACHE II score of < 25 ; 2 organ failures or less).

Note: Drotrecogin alfa can be ordered only after the prescribing critical care attending physician has seen the patient.

Patient Name _____

Date _____ M. R. # _____ ICU Room # _____

Name of physician requesting drotrecogin alfa _____

Name of physician approved the use _____

Step 1. Inclusion criteria (circle all that apply, must meet criteria A or B, plus C and D)

A. APACHE II score must be ≥ 25 and at least 1 of criteria in section B

Or:

B. Criteria of acute organ failure (must meet **at least 3** of following 5 criteria)

- Cardiovascular system dysfunction defined as:
 - Shock, and
 - Hypotension, and
 - Need for vasopressor support despite adequate fluid resuscitation
- Renal dysfunction defined as
 - Oliguria (urine output < 0.5 ml/kg of body weight/hour for 1 hour) despite adequate fluid resuscitation
- Respiratory-system dysfunction defined as
 - P_{aO_2}/F_{iO_2} ratio ≤ 250 in the presence of other dysfunctional organs or systems –or–
 - P_{aO_2}/F_{iO_2} ratio ≤ 200 if the lung was the only dysfunctional organ
- Hematological dysfunction defined as
 - Platelet count $< 80,000/\text{mm}^3$ –or–
 - Platelet decreased by 50% from the highest count in the previous 3 days
 - Thrombocytopenia must be attributable to sepsis rather than medication or other disease
- Unexplained metabolic acidosis with elevated lactic acid concentrations

And:

C. Infection criteria—known or suspected infection (**1 or more** below)

- White cells in a normally sterile body fluid –or–
- Perforated viscus –or–
- Radiographic evidence of pneumonia with purulent sputum –or–
- Syndrome associated with high degree of infection (i.e., ascending cholangitis) –or–
- Focus of infection has been visualized (surgical findings, purulent wound drainage, CT showing evidence of abscess)

D. Modified SIRS criteria (must meet **3 of the 4** criteria below)

- Core temperature $\geq 38^\circ\text{C}$ (100.4°F) or $\leq 36^\circ\text{C}$ (96.8°F) –or–
- Heart rate ≥ 90 bpm (except other medical explanation, treatment to prevent tachycardia) –or–

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- c. Respiratory rate of ≥ 20 breaths/min or $Paco_2$ of ≤ 32 mm Hg or the use of mechanical ventilation for an acute respiratory process –or–
- d. White cell count $\geq 12,000/mm^3$ or $\leq 4,000/mm^3$ or a differential count showing $>10\%$ immature neutrophils

Step 2. Contraindications (please circle):

Drotrecogin alfa increases the risk of bleeding. Drotrecogin alfa is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity:

1. Active internal bleeding
2. Recent (within 3 months) hemorrhagic stroke
3. Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
4. Trauma with an increased risk of life-threatening bleeding
5. Presence of an epidural catheter
6. Intracranial neoplasm or mass lesion or evidence of cerebral herniation
7. Known hypersensitivity to drotrecogin alfa or any component of the product

Step 3. Warnings (please circle):

No data are available in the following clinical situations; therefore, drotrecogin alfa should be used only if the benefits greatly outweigh the risks at the discretion of the critical care attending physician.

1. Patients who are not expected to survive for 28 days due to a pre-existing, non-sepsis related medical condition
2. Age <18 years or weight >135 kg
3. HIV-positive patients whose most recent CD4+ count was $\leq 50/mm^3$
4. Chronic renal failure requiring hemodialysis or peritoneal dialysis
5. Patients who had undergone bone marrow, lung, liver, pancreas, or small-bowel transplantation
6. Pregnancy or breast-feeding
7. Concurrent therapeutic unfractionated heparin (≥ 15 units/kg per hour) or therapeutic low-molecular-weight heparin
8. Platelet count $<30,000 \times 10^6/L$, even if the platelet count is increased after transfusions
9. Prothrombin time: INR > 3.0
10. Recent (within 6 weeks) gastrointestinal bleeding
11. Recent administration (within 3 days) of thrombolytic therapy
12. Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
13. Recent administration (within 7 days) of aspirin > 650 mg/day or other platelet inhibitors
14. Recent (within 3 months) ischemic stroke
15. Intracranial arteriovenous malformation or aneurysm
16. Known bleeding diathesis
17. Chronic severe hepatic disease
18. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.
19. Known hypercoagulable conditions:
 - resistance to activated protein C
 - hereditary deficiency of protein C, protein S, or antithrombin III
 - presence of anticardiolipin antibody, antiphospholipid antibody, lupus anticoagulant, or homocysteinemia; or recently documented (within 3 months)
 - highly suspected deep-vein thrombosis or pulmonary embolism
20. Known or suspected portosystemic hypertension, chronic jaundice, cirrhosis, or chronic ascites
21. Acute pancreatitis with no established source of infection
22. Moribund state in which death was perceived to be imminent
23. Patient **not located in an ICU** (unless ICU admission pending)
24. Patient's family, physician, or both not in favor of aggressive treatment or presence of advance directive to withhold life-sustaining treatment

Step 4. Call any of the following physicians for final approval of drotrecogin alfa use (the person approving drug use will notify the pharmacy that drug may be released)

- Pulmonary/Critical Care Fellow
- Pulmonary/Critical Care Attending

Step 5. Complete drotrecogin alfa dosing orders

1. Pharmacy orders:

- a. Patient weight = _____ kg (use actual body weight (ABW) unless patient is obese; suggested dosing weight for obese patients: $IBW + 0.4 (ABW - IBW)$)
- b. Start drotrecogin alfa @ 24 mcg/kg per hour continuous infusion for total duration of 96 hours

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2. Laboratory orders:

Prior to starting drotrecogin alfa infusion, please obtain:

- Blood cultures $\times 2$ if not done within the previous 48 hours
- Serum pregnancy test Y N (circle one)

3. Nursing considerations:

- Infuse drotrecogin alfa for a cumulative total of 96 hours.
- 0.9% sodium chloride is used for preparation of I.V. drotrecogin alfa bags; do not infuse with any other medications.
- If the patient is being transfused within 2 units of packed cells due to an acute bleed, please notify attending physician immediately.
- If the patient is to have any invasive procedure performed, including the changing of a line over a guidewire, chest tube placement, any operative procedure, or central line insertion, please notify the attending physician and discontinue the drotrecogin alfa, as noted on the "**guidelines for stopping the infusion.**" If drotrecogin alfa has been interrupted for over 1 hour, the time will need to be added to the end of the infusion for a total infusion equal to 96 hours.
- Notify the attending physician for further instructions if the patient requires hemodialysis or renal replacement therapy (CVVH, CVVHD, CAVH, CAVHD).
- Each bag of drotrecogin alfa can be hung no more than **12 hours** from the time of preparation in the pharmacy.
- If therapeutic anticoagulation is indicated for the patient, discontinue drotrecogin alfa and notify the attending physician immediately.

Step 6. Guidelines for stopping drotrecogin alfa infusion

Should clinically important bleeding occur, immediately stop the infusion of drotrecogin alfa. Continued use of other agents affecting the coagulation system should be carefully assessed. Drotrecogin alfa should be discontinued 2 hours prior to undergoing an invasive surgical procedure or procedures with an inherent risk of bleeding. Once adequate hemostasis has been achieved, initiation of drotrecogin alfa may be reconsidered 12 hours after major invasive procedures or surgery, or may be restarted immediately after uncomplicated, less invasive procedures.

APACHE = Acute Physiology and Chronic Health Evaluation; bpm = beats per minute; CAVH = continuous arteriovenous hemofiltration; CAVHD = continuous arteriovenous hemodialysis; CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodialysis; F_{iO_2} = fraction of inspired oxygen; INR = International Normalized Ratio; IBW = ideal body weight; ICU = intensive-care unit; P_{aO_2} = partial pressure of arterial oxygen; P_{aCO_2} = partial pressure of arterial carbon dioxide; PROWESS = Recombinant Activated Human Protein C Worldwide Evaluation in Severe Sepsis; SIRS = systemic inflammatory response syndrome.

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