

# Consensus Developed Drotrecogin alfa (activated) Patient Selection Guideline

**Drotrecogin alfa (activated):** It is recommended that drotrecogin alfa (activated) therapy be strongly considered for all patients with severe sepsis and acute organ dysfunction who have a high risk of death (e.g. as determined by APACHE II). This agent will be in addition to standard supportive measures (i.e. antimicrobials, inotropes, vasopressors, fluids)

## Candidates for drotrecogin alfa (activated)

**A. It is recommended that all patients with severe sepsis should receive drotrecogin alfa (activated) if they present with:**

1. Known or suspected infection. Defined as:
  - Positive cultures  
or
  - Any one of the following:
    - White cells in a normally sterile body fluid
    - Perforated viscus
    - Radiographic evidence of pneumonia in association with the production of purulent sputum

**AND**
2. Three or more signs of SIRS (systemic inflammatory response syndrome). Patient must meet three of the following four criteria:
  - Core temperature of  $\geq 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) or  $\leq 36^{\circ}\text{C}$  ( $96.8^{\circ}\text{F}$ )
  - Heart rate of  $\geq 90$  beats/minute except in patients with a medical condition known to increase the heart rate or those receiving treatment that would prevent tachycardia
  - Respiratory rate  $\geq 20$  breaths/minute or a  $\text{PaCO}_2 \leq 32$  mm Hg or the use of mechanical ventilation for an acute respiratory process
  - White-cell count of  $\geq 12,000/\text{mm}^3$  or  $< 4,000/\text{mm}^3$  or a differential showing  $>10$  percent immature neutrophils

**AND**
3. At least one organ or system dysfunction. Patient must meet at least one of the following five criteria:
  - Cardiovascular dysfunction: Arterial systolic blood pressure  $\leq 90$  mm Hg or the mean arterial pressure  $\leq 70$  mm Hg for at least one hour despite adequate fluid resuscitation, adequate intravascular volume status or the use of vasopressors in an attempt to maintain a systolic blood pressure of  $\geq 90$  mm Hg or a mean arterial pressure of  $\geq 70$  mm Hg
  - Kidney dysfunction: Urine output  $< 0.5$  ml/kg of body weight/hour for  $>1$  hour, despite adequate fluid resuscitation
  - Respiratory dysfunction: Ratio of  $\text{PaO}_2$  to  $\text{FiO}_2 \leq 250$  in the presence of other dysfunctional organs or systems or  $\leq 200$  if the lung was the only dysfunctional organ
  - Hematologic dysfunction: Platelet count  $< 80,000/\text{mm}^3$  or decreased by 50 percent in the 3 days preceding enrollment
  - Unexplained metabolic acidosis:  $\text{pH} \leq 7.30$  or the base deficit had to be  $\geq 5.0$  mmol/liter in association with a plasma lactate level that was  $>1.5$  times the upper limit of the normal value for the reporting laboratory

**B. It is not recommended that patients with the following conditions receive drotrecogin alfa (activated):**

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

**C.** It is recommended that drotrecogin alfa (activated) should be stored, prepared, and labeled for administration by the Pharmacy Department in order to minimize the likelihood of potential medication errors or misdirected therapy. In the event the Pharmacy Department is not staffed during off-peak hours – the health care system/institution should identify alternative measures to assure these processes. Patients chosen to receive drotrecogin alfa (activated) should receive their first dose within 24 hours of meeting criteria.

**D.** The following considerations should be assessed on an individualized basis when selecting patients for drotrecogin alfa (activated) therapy, including:

1. Platelet counts less than  $30,000 \times 10^6/L$ , even if the platelet count is increased after transfusions
2. Known bleeding diatheses
3. Recent (within 6 weeks) gastrointestinal bleeding
4. Recent (within 3 months) ischemic stroke
5. Chronic severe hepatic disease
6. Intracranial arteriovenous malformation or aneurysm
7. Prothrombin time – INR >3.0
8. Lower disease severity (e.g. such as determined by APACHE II scores)
9. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location
10. Use of the following medications or treatment regimens:
  - Concurrent therapeutic heparin ( $\geq 15$  units/kg/hr)
  - Recent administration (within 3 days) of thrombolytic therapy
  - Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
  - Recent administration (within 7 days) of aspirin >650 mg per day or other platelet inhibitors
  - Low-molecular-weight heparins at a higher dose than recommended for prophylaxis\*
  - Direct thrombin inhibitors\*
  - Antithrombin III (at a dose >10,000 U within the past 12 hours), protein C infusion (within last 24 hours) or other investigational agents known to affect coagulation\*
11. Pregnancy and/or breast feeding
12. Hereditary deficiency of protein C, protein S, or antithrombin III\*
13. Chronic renal failure requiring hemodialysis or peritoneal dialysis\*
14. Known hypercoagulable condition, including resistance to activated protein C\*
15. Anticardiolipin antibody, antiphospholipid lupus anticoagulant, lupus anticoagulant, or homocystinemia\*
16. Recently documented ( $\leq 3$  months) or highly suspected deep-vein thrombosis or pulmonary embolism\*
17. Acute pancreatitis with no established source of infection<sup>1\*</sup>
18. Patients with HIV ( $CD_4 < 50$ )<sup>1\*</sup>
19. History of bone marrow or solid organ transplantation<sup>1\*</sup>
20. Age less than <18 years<sup>2</sup>
21. Weight > 135 kilograms<sup>3\*</sup>

\*These patient groups were excluded in the clinical trial

1 No clinical data currently exists

2 Safety and efficacy has not been established in pediatrics

3 Weight requirement used in clinical trial to ensure adequate drotrecogin alfa (activated) supply