

CLINICAL THERAPEUTICS

Activated Protein C for Sepsis

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.

A 55-year-old man is brought to the emergency department with abdominal pain, fever (temperature, 102.9°F), and dyspnea. His medical history includes an appendectomy 8 years earlier. Abdominal radiography shows free air as well as signs of small-bowel ileus. An emergency laparotomy is performed. Intraoperatively, a lower-small-bowel perforation is identified, with evidence of peritonitis. Partial ileal resection with end-to-end anastomosis is performed. Treatment with broad-spectrum antibiotics is initiated; blood cultures grow typical Enterobacteriaceae (*Escherichia coli* and *Proteus mirabilis*) and *Enterococcus faecium*. Septic shock with hypotension requiring vasopressor support, hypoxemia requiring mechanical ventilation, and renal dysfunction develop, with an elevated serum lactate level. The patient's Acute Physiology and Chronic Health Evaluation (APACHE) II score (see the Supplementary Appendix, available with the full text of this article at NEJM.org) is 27. Results of clotting studies are normal, and no clinical bleeding is detected. The surgeon and the intensivist decide that treatment with activated protein C is indicated.

THE CLINICAL PROBLEM

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Sepsis is a systemic inflammatory response to presumed or known infection.¹ It is a leading cause of in-hospital death in adult patients, and the incidence is increasing worldwide.²⁻⁴ There is considerable variation among countries, yet overall, there is a strong positive correlation between the frequency of sepsis and mortality rates in the intensive care unit (ICU).^{5,6} In a prospective study of 3877 patients in 454 ICUs in Germany, the prevalence of sepsis was 12.4%.⁷ The prevalence of severe sepsis, defined as sepsis associated with organ dysfunction,¹ was 11.0%; nearly half the patients with severe sepsis had septic shock, defined as sepsis with hypotension, despite adequate fluid replacement.¹ The incidence of severe sepsis was estimated to be 76 to 110 cases per year per 100,000 population.⁷ These data are consistent with reports from earlier studies of rates from 51 to 300 cases per year per 100,000 population.^{2,8}

The prognosis for patients with severe sepsis is poor. Mortality rates range from 38%⁹ to 59%.¹⁰ The study from Germany reported mortality rates among ICU patients and among inpatients generally of 48.4% and 55.2%, respectively.⁷ Patients who survive severe sepsis have a lower quality of life than does the age- and sex-adjusted general population, as long as 1.5 years later.¹¹ The economic burden of severe sepsis is immense. In one analysis from Germany, the estimated daily cost of hospital care for a patient with severe sepsis was €1090 (approximately \$1,600), resulting in an overall cost per hospital stay that was 2 to 11 times the average cost per patient.¹²

 PATHOPHYSIOLOGY AND THE EFFECT OF THERAPY

Sepsis is a complex phenomenon that remains incompletely understood. Infectious pathogens possess unique structural components called pathogen-associated molecular patterns; examples include lipopolysaccharide in gram-negative bacteria and peptidoglycan in gram-positive bacteria.¹³ These molecules bind to host cell receptors, or pattern-recognition receptors, including the cell-surface toll-like receptors and several types of cytoplasmic receptors.¹⁴ Receptor binding results in activation of intracellular signaling pathways that lead to a variety of responses, including increased transcription of inflammatory cytokines, up-regulation of adhesion-molecule expression, stimulation of humoral and cell-mediated immune responses, and activation of vascular endothelial cells. A detailed discussion of the pathogenesis of sepsis has been addressed in a number of recent reviews.¹⁵⁻¹⁸

An important feature of the pathophysiology of sepsis is the development of a procoagulant state.^{19,20} Inflammatory cytokines both activate the coagulation cascade and inhibit fibrinolysis. In turn, components of the coagulation and fibrinolytic systems have proinflammatory effects. Disseminated intravascular coagulation, one of the most feared complications of sepsis, is a manifestation of the dysregulation of coagulation.²¹

Protein C is a soluble, vitamin K-dependent, plasma serine protease that plays a central role in endogenous anticoagulation.²² The activated form is generated when thrombin, bound to the cofactor thrombomodulin, interacts with and cleaves the zymogen protein C. Activated protein C is a potent anticoagulant and profibrinolytic enzyme capable of inactivating clotting cofactors Va and VIIIa and plasminogen-activator inhibitor 1 (Fig. 1).^{23,24} Proinflammatory cytokines such as tumor necrosis factor induce a decline in thrombomodulin activity^{25,26} and thus a decrease in the generation of activated protein C. Reduced levels of protein C in patients with sepsis have been correlated with an increase in the risk of death.²⁷⁻³⁰ These observations led to the hypothesis that the administration of activated protein C might be beneficial in patients with sepsis.

There is disagreement about whether the effects of activated protein C in patients with sepsis are primarily due to its anticoagulant activity. There is evidence that activated protein C is also

an important inhibitor of the systemic inflammatory response in patients with severe sepsis.^{22,31} In addition, activated protein C has been reported to inhibit nitric oxide-induced vascular dysfunction, apoptosis of lymphocytes and endothelial cells, and activation of neutrophils. In studies of animals, genetically engineered forms of activated protein C with minimal anticoagulant activity retain the beneficial effects of the innate type, with a diminished risk of bleeding.³² In contrast, in animal models of peritonitis and pneumonia, the beneficial effects of activated protein C are associated with its anticoagulant effects.^{33,34} In clinical trials, other agents with antithrombotic effects (e.g., recombinant tissue factor pathway inhibitor and antithrombin III) have had no effect on the mortality rate among patients with sepsis.^{35,36}

 CLINICAL EVIDENCE

The first clinical study of activated protein C was a phase 2 dose-ranging trial of a recombinant human activated protein C called drotrecogin alfa (activated) (DrotAA; Xigris, Eli Lilly) in patients with severe sepsis. Administration of DrotAA resulted in dose-dependent reductions in D-dimer and interleukin-6 levels without an increase in serious bleeding.³⁷

These results were used to select a DrotAA dose of 24 μ g per kilogram of body weight per hour for use in the subsequent phase 3 Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study.³⁸ This placebo-controlled, randomized, double-blind, multicenter trial included 1690 patients, approximately 75% of whom had multiorgan dysfunction. Treatment with DrotAA within 24 hours after diagnosis was associated with a mortality rate of 24.7% at 28 days versus 30.8% with placebo ($P=0.005$). As reported subsequently,³⁹ the overall incidence of at least one bleeding event was 24.9% in the treatment group and 17.7% in the placebo group ($P=0.001$). The incidence of serious bleeding in the PROWESS study was also higher in the DrotAA group than in the placebo group (3.5% vs. 2.0%, $P=0.06$). In subgroup analyses, most of the benefit of DrotAA treatment was seen in patients at increased risk for death, including those with APACHE II scores of 25 or greater.⁴⁰ On the basis of these data, in 2001, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency ap-

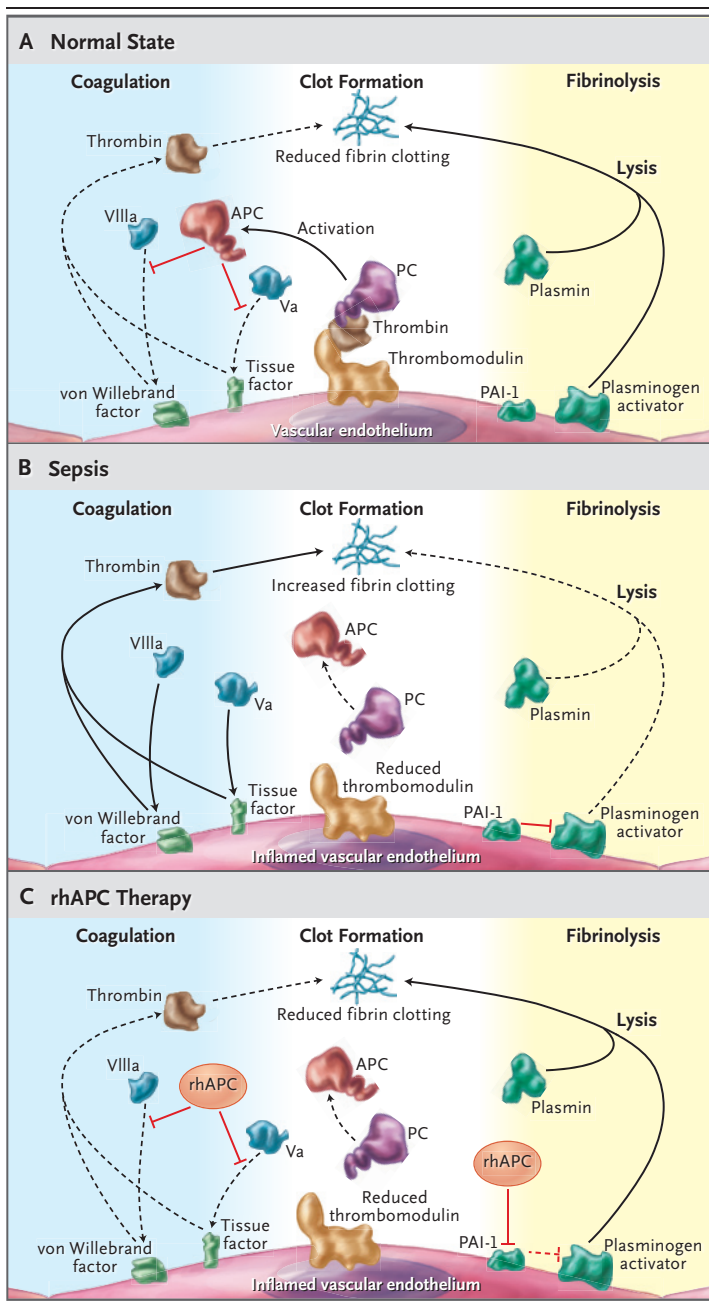


Figure 1. The Procoagulant State in Patients with Sepsis and the Mode of Action of Recombinant Human Activated Protein C (rhAPC).

In the normal state (Panel A), the vascular endothelial cell expresses thrombomodulin, which, after coupling to thrombin, allows a feedback loop of inhibition of thrombin formation by inducing the production of activated protein C (APC) from soluble protein C (PC). APC inhibits Va and VIIIa, important cofactors of the extrinsic and intrinsic procoagulant pathway, respectively. Thus, in the normal state, anticoagulation predominates to maintain blood flow. In addition, plasminogen activator, expressed on the cell surface, initiates fibrinolysis, thus reducing clot formation. Panel B shows the host response to infection, in which endothelial cells are activated by inflammatory mediators. Thrombomodulin expression is markedly reduced, making APC-dependent anticoagulation inefficient. Fibrinolysis is inhibited by the cytokine-induced expression of plasminogen-activator inhibitor 1 (PAI-1). As a result, the increased expression of tissue factor and von Willebrand factor leads to clot formation and disseminated intravascular coagulation. Panel C shows the results of administration of rhAPC in patients with sepsis. The rhAPC replaces physiologic APC, inhibits further clot formation, and increases fibrinolysis by blocking PAI-1. Procoagulant activity is reduced. The red T symbols indicate inhibition, and the dashed arrows and T symbols indicate actions that would be present in the absence of the inhibition or conditions shown.

of cells for growing the recombinant DrotAA protein. It was also suggested that, in practice, the APACHE II score would be difficult to determine consistently and would change during the early period of care and that the use of a subgroup analysis of data from a major trial to identify suitable candidates for treatment was not appropriate.

The FDA defended its decision to approve DrotAA⁴³ but obtained commitments from Eli Lilly to conduct additional trials to try to resolve some of the questions raised. The Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trial evaluated the role of DrotAA therapy in patients with severe sepsis, associated with either single-organ failure or an APACHE II score below 25.⁴⁴ The study was stopped, after enrolling 2640 patients, because there was no indication of a positive effect. The 28-day rate of death from any cause was 18.5% in the DrotAA group and 17% in the placebo group ($P=0.34$). The in-hospital mortality rate was 20.6% in the DrotAA group and 20.5% in the placebo group ($P=0.98$). Serious bleeding occurred in 2.4% of patients receiving DrotAA,

proved the use of DrotAA in patients with severe sepsis who are at increased risk for death.

The decision to approve DrotAA was the subject of criticism by some experts.^{41,42} It was noted that, during the course of the PROWESS trial, some changes had been made in the protocol, among them the exclusion of participants who were thought to be likely to die within 28 days because of the severity of the underlying disease and the introduction of a new master lot

as compared with 1.2% of patients receiving placebo ($P=0.02$) during the drug-infusion period. No significant difference was observed in the rate of hemorrhage involving the central nervous system (0.3% with DrotAA and 0.2% with placebo).⁴⁴ A randomized study of DrotAA therapy in children also showed no significant benefit.⁴⁵

Critics concluded that a general recommendation for the clinical use of DrotAA was premature or not justified.^{46,47} However, other investigators, including the members of the Surviving Sepsis Campaign, suggested that the use of DrotAA was reasonable for patients who have multiorgan failure or a high risk of death.⁴⁸ Another large, multicenter, randomized clinical trial is currently enrolling patients (the Efficacy and Safety of Drotrecogin Alfa [Activated] in Adult Patients with Septic Shock study; ClinicalTrials.gov number, NCT00604214). The results of this clinical trial could substantially affect our assessment of when and how to use this drug.

CLINICAL USE

In cases of severe sepsis, treatment of the underlying cause of infection requires early and meticulous attention to the potential site of infection, including the use of antimicrobial agents and, if appropriate, surgical drainage. Physiological support for organ dysfunction with the use of inotropes, mechanical ventilation, and renal-replacement therapy should be instituted in certain clinical circumstances. Corticosteroids are broadly used, although their benefit remains uncertain.^{49,50} The use of DrotAA should therefore be considered part of a more extensive strategy of critical care management.

The results of the PROWESS trial have led to the increasing use of DrotAA by clinicians⁵¹; however, surveys have revealed that its use in clinical practice is not consistent with the inclusion and exclusion criteria of the PROWESS study, mostly because the initiation of therapy is often delayed in practice.^{52,53} The use of DrotAA should be limited to patients who have severe sepsis with evidence of dysfunction of more than one organ, which should be assessed by means of validated scoring systems such as the Sequential Organ Failure Assessment (SOFA) score⁵⁴ (see the Supplementary Appendix), and an APACHE II score of 25 or higher. The drug should not be used in adults who have sepsis

associated with a low risk of death or with single-organ (not multiorgan) dysfunction, nor should it be used in children. To ensure consistent application of these criteria, we evaluate patients for DrotAA therapy using a standardized checklist, which includes not only the APACHE II score and the SOFA score but also absolute and relative contraindications (see below).

The PROWESS trial established strict exclusion criteria to limit the risk of bleeding with DrotAA treatment (see the Supplementary Appendix). There is a general consensus that patients who have known hemorrhage, have undergone intracranial surgery, or have a severe head injury should be strictly excluded from treatment with DrotAA. The risk of bleeding during other surgical procedures should be assessed individually; for instance, we are very reluctant to use DrotAA in patients after thoracotomy or in patients with clinically relevant soft-tissue injuries. DrotAA therapy should not be restarted or initiated for 12 hours after any major surgical procedure. The patient's coagulation variables (prothrombin time and partial thromboplastin time) should be within the normal range, and the platelet count should not be less than 30,000 per cubic millimeter.

The dose of DrotAA, as in the PROWESS protocol, should be 24 μ g per kilogram of body weight per hour, administered as a continuous infusion over a period of 96 hours. A post hoc analysis of data from five trials involving patients with severe sepsis suggested that the benefit of DrotAA is greater with earlier administration.⁵⁵ Recent guidelines (see below), as well as protocols of ongoing studies,⁵⁶ recommend that DrotAA therapy be initiated within 24 hours after the onset of severe sepsis. The same dose and infusion rate are recommended, regardless of the severity of organ dysfunction, type of infection, or presence or absence of coexisting conditions. No direct drug-drug interactions have been identified. Use of low-dose heparin as prophylaxis against deep venous thrombosis should not be discontinued during DrotAA infusion. However, patients requiring moderate or high doses of heparin should not be treated with DrotAA.

At present, there are no recommendations for individual dose adjustment on the basis of laboratory values during the 96-hour infusion period. Nonetheless, it is recommended that the results of standard clotting tests and platelet counts be

monitored to identify unexpected risks of bleeding as promptly as possible. Slight increases in the prothrombin time or decreases in the D-dimer level may occur but are not reasons to adjust the treatment if there is no sign of clinical bleeding. However, if severe bleeding occurs during the infusion, therapy should be discontinued immediately and should not be reinitiated.

The overall cost of treatment with DrotAA is approximately \$7,500 to \$9,000.⁵⁷⁻⁵⁹ Some insurance programs provide full reimbursement and others provide partial reimbursement; some hospitals include the cost of DrotAA in the general budget for the ICU.

ADVERSE EFFECTS

In the major clinical trials, administration of DrotAA in patients with sepsis increased the risk of bleeding, primarily during the infusion period.^{36,60} Over the 28-day study period, serious bleeding events — the occurrence of which was often correlated with the a greater severity of sepsis at baseline and with a platelet count below 30,000 per cubic millimeter during the infusion period — were observed in 3.5 to 6.5% of patients receiving DrotAA as compared with 2.0 to 5.0% of patients receiving placebo.⁶⁰ Rates of bleeding involving the central nervous system were 0 to 1.5% with DrotAA as compared with 0 to 0.7% with placebo.

The risk of bleeding has been somewhat higher in clinical practice than in the major clinical trials. In studies in Canada and Italy, the reported rates of serious bleeding were 10% and 10.9%, respectively.^{52,53} In the Canadian study, risk factors for bleeding included failure of four or more organs and the presence of a relative contraindication to DrotAA therapy.⁵² These findings underscore the importance of careful consideration of the exclusion criteria used in the PROWESS trial that are related to the risk of bleeding (see the Supplementary Appendix). Close clinical monitoring for bleeding is also essential, including assessment of the score on the Glasgow Coma Scale for early recognition of possible hemorrhage involving the central nervous system.

AREAS OF UNCERTAINTY

Several areas of uncertainty with regard to DrotAA treatment have been described in the sections

above, but three of these areas are of particular importance. First, the efficacy of DrotAA remains a matter of dispute. Second, although the benefit of DrotAA may be a consequence of its anticoagulant properties, an important role of other physiological effects has been suggested. Third, the optimal application of the PROWESS exclusion criteria (see the Supplementary Appendix) is uncertain.

The appropriate application of inclusion criteria for the selection of patients is also a key issue. The subgroup analysis in the PROWESS trial suggested that all patients with an APACHE II score of 25 or greater would benefit.⁴⁰ In contrast, the ADDRESS trial suggested that patients with an APACHE II score of less than 25 or with single-organ failure would not benefit.⁴⁴ The conservative interpretation of these data is to require both an APACHE II score of 25 or higher and dysfunction of more than one organ.

GUIDELINES

In 2004, the first Surviving Sepsis Campaign guidelines included the following recommendation: “rhAPC [recombinant human activated protein C] (DrotAA) is recommended in patients at high risk of death (APACHE II ≥ 25 , sepsis-induced multiple organ failure, septic shock, or sepsis-induced ARDS [acute respiratory distress syndrome]) and no absolute contraindication related to bleeding risk or relative contraindication that outweighs the potential benefit of rhAPC.”⁴⁸ A similar recommendation was included in the Guidelines of the German Sepsis Society in 2006.⁶¹

These recommendations came under criticism for the way in which they were developed.⁶² More than 90% of the funding of the Surviving Sepsis Campaign was provided by Eli Lilly, and it was asserted that the guidelines were orchestrated as an extension of their marketing campaign for DrotAA.

As a result of this controversy, industry sponsorship was not permitted when the guidelines underwent revision. The 2008 guidelines downgraded the recommendation for DrotAA therapy, using the word “suggest” rather than “recommend”: “We suggest that adult patients with sepsis induced organ dysfunction associated with a clinical assessment of high risk of death, most of whom will have APACHE II ≥ 25 or multiple

organ failure, receive rhAPC if there are no contraindications (Grade 2B except for patients within 30 days of surgery where it is Grade 2C). Relative contraindications should also be considered in decision making.”⁶³

RECOMMENDATIONS

The patient described in the vignette is an appropriate candidate for therapy with DrotAA on the basis of the severity of his septic state (APACHE II score of 27) and the presence of multiorgan dysfunction (cardiovascular, pulmonary, and renal). His recent surgical procedure (the emergency laparotomy) is a relative contraindication.

However, if he has no clinical evidence of bleeding and has normal coagulation values, and if his platelet count is not less than 30,000 per cubic millimeter, we would favor the use of DrotAA. Therapy should be initiated as promptly as possible, since there is convincing evidence that the benefit begins to wane 24 hours after the onset of sepsis. The patient's symptoms should be monitored and the coagulation values obtained daily during the treatment period; we would interrupt the DrotAA infusion immediately if bleeding occurs.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Toussaint S, Gerlach H. Activated protein C for sepsis. N Engl J Med 2009;361:2646-52.

THE APACHE II SEVERITY OF DISEASE CLASSIFICATION SYSTEM

| PHYSIOLOGIC VARIABLE | HIGH ABNORMAL RANGE | | | | | LOW ABNORMAL RANGE | | | |
|--|---------------------|----------------|--------------|------------------|---------------------------|----------------------------|----------------|----------------------------|---------------------------|
| | +4 | +3 | +2 | +1 | 0 | +1 | +2 | +3 | +4 |
| TEMPERATURE — rectal (°C) | ≥ 41° ○ | 39°-40.9° ○ | | 38.5°-38.9° ○ | 36°-38.4° ○ | 34°-35.9° ○ | 32°-33.9° ○ | 30°-31.9° ○ | ≤ 29.9° ○ |
| MEAN ARTERIAL PRESSURE — mm Hg | ≥ 160 ○ | 130-159 ○ | 110-129 ○ | | 70-109 ○ | | 50-69 ○ | | ≤ 49 ○ |
| HEART RATE (ventricular response) | ≥ 180 ○ | 140-179 ○ | 110-139 ○ | | 70-109 ○ | | 55-69 ○ | 40-54 ○ | ≤ 39 ○ |
| RESPIRATORY RATE — (non-ventilated or ventilated) | ≥ 50 ○ | 35-49 ○ | | 25-34 ○ | 12-24 ○ | 10-11 ○ | 6-9 ○ | | ≤ 5 ○ |
| OXYGENATION: A-aDO ₂ or PaO ₂ (mm Hg) | | | | | | | | | |
| a. FIO ₂ ≥ 0.5 record A-aDO ₂ | ≥ 500 ○ | 350-499 ○ | 200-349 ○ | | < 200 ○ | | | | |
| b. FIO ₂ < 0.5 record only PaO ₂ | | | | | PO ₂ > 70 ○ | PO ₂ 61-70 ○ | | PO ₂ 55-60 ○ | PO ₂ < 55 ○ |
| ARTERIAL pH | ≥ 7.7 ○ | 7.6-7.69 ○ | | 7.5-7.59 ○ | 7.33-7.49 ○ | | 7.25-7.32 ○ | 7.15-7.24 ○ | < 7.15 ○ |
| SERUM SODIUM (mMol/L) | ≥ 180 ○ | 160-179 ○ | 155-159 ○ | 150-154 ○ | 130-149 ○ | | 120-129 ○ | 111-119 ○ | ≤ 110 ○ |
| SERUM POTASSIUM (mMol/L) | ≥ 7 ○ | 6-6.9 ○ | | 5.5-5.9 ○ | 3.5-5.4 ○ | 3-3.4 ○ | 2.5-2.9 ○ | | < 2.5 ○ |
| SERUM CREATININE (mg/100 ml) (Double point score for acute renal failure) | ≥ 3.5 ○ | 2-3.4 ○ | 1.5-1.9 ○ | | 0.6-1.4 ○ | | < 0.6 ○ | | |
| HEMATOCRIT (%) | ≥ 60 ○ | | 50-59.9 ○ | 46-49.9 ○ | 30-45.9 ○ | | 20-29.9 ○ | | < 20 ○ |
| WHITE BLOOD COUNT (total/mm ³) (in 1,000s) | ≥ 40 ○ | | 20-39.9 ○ | 15-19.9 ○ | 3-14.9 ○ | | 1-2.9 ○ | | < 1 ○ |
| GLASGOW COMA SCORE (GCS): Score = 15 minus actual GCS | | | | | | | | | |
| A Total ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variable points | | | | | | | | | |
| Serum HCO ₃ (venous-mMol/L) [Not preferred, use if no ABGs] | ≥ 52 ○ | 41-51.9 ○ | | 32-40.9 ○ | 22-31.9 ○ | | 18-21.9 ○ | 15-17.9 ○ | < 15 ○ |

B AGE POINTS:

Assign points to age as follows:

| AGE(yrs) | Points |
|----------|--------|
| ≤ 44 | 0 |
| 45-54 | 2 |
| 55-64 | 3 |
| 65-74 | 5 |
| ≥ 75 | 6 |

C CHRONIC HEALTH POINTS

If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:

- for nonoperative or emergency postoperative patients — 5 points
- for elective postoperative patients — 2 points

DEFINITIONS

Organ Insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria:

LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

CARDIOVASCULAR: New York Heart Association Class IV.

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respirator dependency.

RENAL: Receiving chronic dialysis.

IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

APACHE II SCORE

Sum of **A** + **B** + **C** :

A APS points _____

B Age points _____

C Chronic Health points _____

Total APACHE II _____

| | | SOFA Score | | | | |
|--|----------------|---------------|---|---|--|---|
| | | 0 | 1 | 2 | 3 | 4 |
| Respiration | | | | | | |
| Pao ₂ /Fio ₂ (torr) | >400 | ≤400 | ≤300 | ≤200 With respiratory support | ≤100 With respiratory support | |
| Coagulation | | | | | | |
| Platelets (×10 ³ /mm ³) | >150 | ≤150 | ≤100 | ≤50 | ≤20 | |
| Liver | | | | | | |
| Bilirubin (mg/dL) | <1.2 | 1.2–1.9 | 2.0–5.9 | 6.0–11.9 | >12.0 | |
| (μmol/L) | <20 | 20–32 | 33–101 | 102–204 | >204 | |
| Cardiovascular | | | | | | |
| Hypotension | No hypotension | MAP <70 mm Hg | Dopamine ≤5 or dobutamine (any dose) ^a | Dopamine >5 or epi ≤0.1 or norepi ≤0.1 ^a | Dopamine >15 or epi >0.1 or norepi >0.1 ^a | |
| Central Nervous System | | | | | | |
| Glasgow Coma Score | 15 | 13–14 | 10–12 | 6–9 | <6 | |
| Renal | | | | | | |
| Creatinine (mg/dL) | <1.2 | 1.2–1.9 | 2.0–3.4 | 3.5–4.9 | >5.0 | |
| (μmol/L) | <110 | 110–170 | 171–299 | 300–440 | >440 | |
| or urine output | | | | or <500 mL/day | or <200 mL/day | |

epi, epinephrine; norepi, norepinephrine.

^aAdrenergic agents administered for at least 1 hr (doses given are in μg/kg/min).

To convert torr to kPa, multiply the value by 0.1333.

**Exclusion Criteria from the PROWESS Trial to
reduce risk of bleeding with DrotAA treatment³⁸**

- Platelet Count $<30,000/\text{mm}^3$.
- Surgery requiring general or spinal anesthesia within 12 hours before the infusion.
- Potential need for such surgery during the infusion.
- Evidence of active bleeding postoperatively.
- History of severe head trauma requiring hospitalization.
- Intracranial surgery.
- Stroke within 3 months before treatment.
- Any history of intracerebral arterio-venous malformation.
- Cerebral aneurysm.
- Mass lesion of the central nervous system.
- History of congenital bleeding diathesis.
- Gastrointestinal bleeding within 6 weeks before treatment unless corrective surgery had been performed.
- Trauma considered to increase the risk of bleeding.
- Unfractionated heparin to treat an active thrombotic event within 8 hours before the infusion; prophylactic treatment with a dose of unfractionated heparin of up to 15,000 U per day is permitted. Prophylactic doses $>15,000$ U per day have to be stopped within 12 hours before infusion.
- Warfarin (if used within 7 days before treatment and if the prothrombin time exceeds the upper limit of the normal range for the institution).
- Acetylsalicylic acid at a dose of more than 650 mg/day within 3 days before the treatment.
- Thrombolytic therapy within 3 days before treatment.
- Glycoprotein IIb/IIIa antagonists within 7 days before study entry.
- Antithrombin III at a dose of more than 10,000 U within 12 hours before treatment.
- Protein C within 24 hours before treatment.