

Guidance on patient identification and administration of recombinant human activated protein C for the treatment of severe sepsis

Gary Garber MD FRCPC¹, RT Noel Gibney MB FRCPC², Bruce Light MD FRCPC³,
 Claudio Martin MD FRCPC⁴, Kenneth Cunningham MD FRCPC⁵,
 Jean-Gilles Guimond MD FRCPC⁶, Sheldon Magder MD FRCPC⁷,
 James Russell MD FRCPC⁸

G Garber, RTN Gibney, B Light, et al. Guidance on patient identification and administration of recombinant human activated protein C for the treatment of severe sepsis. *Can J Infect Dis* 2002;13(6):361-372.

Approximately one-third of cases of severe sepsis result in death. Endogenous activated protein C (APC) plays a key role in the regulation of the inflammation, fibrinolysis and coagulation associated with severe sepsis. In a recently published phase III trial, Protein C Worldwide Evaluation in Severe Sepsis (PROWESS), intravenous administration of recombinant human APC (rhAPC) 24 µg/kg/h for 96 h to patients with severe sepsis resulted in a 6.1% reduction in absolute mortality and a 19.4% reduction in the relative risk of death from any cause within 28 days (number needed to treat = 16). This dose is now being applied in clinical practice.

rhAPC is recommended for the treatment of severe sepsis (sepsis associated with acute organ dysfunction) occurring as a result of all types of infection (Gram-negative bacterial, Gram-positive bacterial and fungal). A panel of Canadian clinicians experi-

enced in the treatment of severe sepsis and the management of critical care patients has developed this consensus document to assist clinicians in appropriate patient selection and management of potential challenges associated with rhAPC therapy.

Key Words: *Coagulation; Recombinant human activated protein C; Sepsis; Septic shock*

Directives sur l'identification des patients et l'administration de protéine C activée humaine recombinante pour le traitement de la septicémie grave

RÉSUMÉ : La septicémie grave est fatale dans environ le tiers des cas. La protéine C activée (PCA) endogène joue un rôle essentiel dans la régulation de l'inflammation, de la fibrinolyse et de la coagulation associées à la septicémie grave. Dans l'essai de phase III récemment publié, Protein C

Suite à la page suivante

¹Department of Medicine, University of Ottawa, Ottawa, Ontario; ²Division of Critical Care Medicine, University of Alberta, Edmonton, Alberta; ³Medicine and Medical Microbiology, University of Manitoba and St Boniface General Hospital, Winnipeg, Manitoba; ⁴University of Western Ontario and London Health Sciences Center, London, Ontario; ⁵Department of Medicine and Critical Care, Lion's Gate Hospital, Vancouver, British Columbia; ⁶Department of Medicine, Université de Montréal, CHUM, Montreal, Quebec; ⁷Department of Medicine, McGill University and Royal Victoria Hospital, Montreal, Quebec; ⁸Department of Medicine, University of British Columbia and St Paul's Hospital, Vancouver, British Columbia

Correspondence and reprints: Dr Gary Garber, Head, Division of Infectious Diseases, The Ottawa Hospital – General Campus, 501 Smyth Road, Room G-8, Ottawa, Ontario K1H 8L6. Telephone 613-737-8173, fax 613-737-8099, e-mail ggarber@ottawahospital.on.ca

Received for publication May 10, 2002. Accepted August 16, 2002

Worldwide Evaluation in Severe Sepsis (PROWESS), l'administration intraveineuse de PCA humaine recombinante (PCAh_r) à raison de 24 µg/kg/h pendant 96 heures à des patients atteints de septicémie grave a entraîné une réduction de la mortalité absolue de 6,1 % et une réduction de 19,4 % du risque relatif de décès de toutes causes dans les 28 jours (nombre de patients qu'il faut traiter = 16). C'est la dose désormais utilisée en pratique clinique. La PCAh_r est recommandée pour le traitement

de la septicémie grave (avec dysfonctionnement aigu des organes) résultant de tous les types d'infections, bactériennes Gram négatif ou Gram positif et fongiques. Ce document de consensus a été élaboré par un groupe de cliniciens canadiens possédant de l'expérience dans le traitement de la septicémie grave et la prise en charge des patients aux soins intensifs afin d'aider les cliniciens à effectuer une sélection appropriée des patients et à faire face aux défis potentiels du traitement par la PCAh_r.

DEVELOPMENT OF THIS GUIDANCE DOCUMENT

The purpose of the present document is to provide guidance on the use of recombinant human activated protein C (rhAPC) in the treatment of severe sepsis. All subsequent reference to rhAPC is based on the use of drotrecogin alpha (activated). The United States Food and Drug Administration (FDA) has reviewed and approved drotrecogin alfa (activated) for use in the treatment of severe sepsis in the United States, and it is currently under review by Health Canada.

This document reflects the consensus opinions of the authors and is based on the available data to date. It is not intended as a formal set of practice guidelines, and such a process was not used in the development of the paper. Nor is it intended for use in place of the product monograph for rhAPC, but as an additional resource. Clinicians must keep in mind that providing optimal supportive care is an important aspect in the management and treatment of severe sepsis. Because the focus of these recommendations is rhAPC, readers should consult other documents for further information on supportive care.

The inclusion and exclusion criteria used in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study were defined to meet regulatory requirements for a multicentre clinical trial. The strict application of these criteria could preclude the use of rhAPC in patients for whom the drug may be both safe and beneficial. For this reason, the authors sought to provide guidance in some important grey areas for the use of rhAPC in severe sepsis where no data exist or clinical experience is limited. A number of frequently asked questions associated with the use of rhAPC are also addressed. As further data become available, these opinions may change and this guidance document will be updated accordingly.

SEPSIS: BACKGROUND

Sepsis remains a leading cause of mortality despite ongoing advancements in critical care. In the United States, over 700,000 cases of severe sepsis are reported each year, of which nearly one-third are fatal (1). Sepsis refers to the systemic response to infection, which is triggered by the patient's immune responses to various components of an invading organism. The condition is associated with a marked overstimulation of the patient's inflammatory, antifibrinolytic and procoagulant systems. In severe sepsis, the overstimulation of these systems results in organ dysfunction. Severe sepsis is, therefore, the cause of substantial

morbidity and mortality, and increased healthcare costs (2). The incidence of sepsis is likely to increase due to several factors, including an aging population, an increased number of immunocompromised hosts (eg, cancer patients, transplant patients), a rising incidence of nosocomial infections, and increased resistance of microorganisms to antibiotic therapies.

The pathogenesis of severe sepsis involves an interaction between the patient's inflammatory, fibrinolytic and coagulation pathways (3). The presence of lipopolysaccharides or exotoxins from Gram-positive organisms, or an increase in inflammatory cytokines, such as tumour necrosis factor alpha (TNF-α), interleukin (IL)-1 and IL-6, induces a procoagulant and antifibrinolytic state. In addition, multiple proinflammatory pathways may be activated by the procoagulant, thrombin. Microvascular thrombosis may cause tissue ischemia that contributes to organ dysfunction during severe sepsis. The severity of organ dysfunction strongly correlates with the degree of coagulopathy that develops. Attempts to control sepsis via the inhibition of TNF-α and IL-1 production (among other therapeutic approaches) have proven unsuccessful to date, possibly because of an earlier, unrecognized importance of the coagulation cascade in the pathogenesis of severe sepsis.

Endogenous activated protein C (APC) plays a key role in the regulation of the inflammation, fibrinolysis and coagulation associated with severe sepsis (Figure 1). Upon conversion from its inactivated state, APC inhibits factors Va and VIIIa. APC also inhibits two key proteins involved in the suppression of fibrinolysis, plasminogen activator inhibitor 1 and thrombin activatable fibrinolysis inhibitor, and inhibits the production of proinflammatory cytokines such as TNF-α, IL-1 and IL-6 (4-9). The conversion of inactive protein C to APC is mediated in part through thrombin bound to its endothelial-binding protein, thrombomodulin (TM). During severe sepsis, APC production is reduced because of the downregulation of TM by proinflammatory cytokines, resulting in a net deficit of APC in patients with severe sepsis, a condition associated with an increased risk of death (10-13).

Because of its anticoagulant, anti-inflammatory and profibrinolytic properties, and its deficiency in severe sepsis, it was postulated that treatment with APC may be beneficial in the treatment of coagulopathy and inflammation in patients with severe sepsis. In a phase II clinical trial, an infusion of rhAPC in patients with severe sepsis was associated with a reduction in the severity of coagulopathy and inflammation, as assessed by reductions in serum levels of D-dimer and IL-6 (14). Moreover, in experiments using a

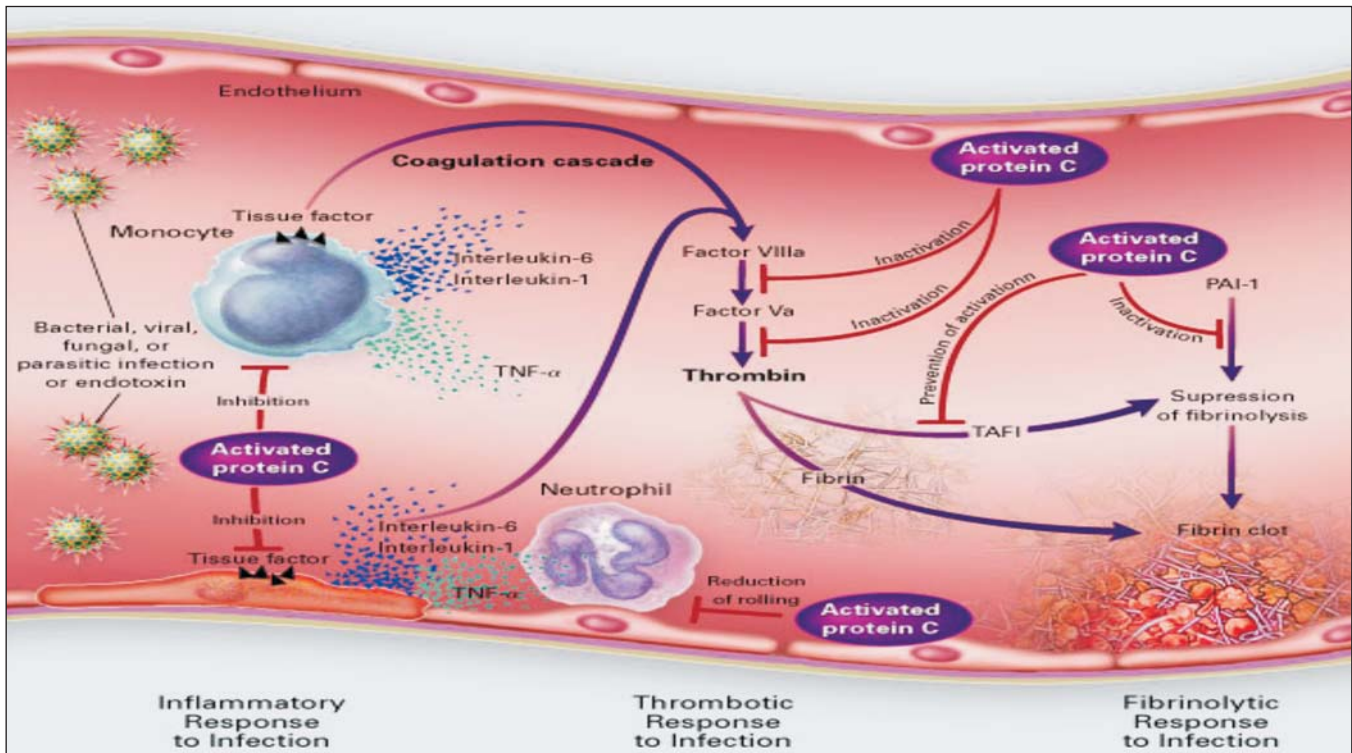


Figure 1) The role of inflammation, fibrinolysis and coagulation in infection. The inflammatory and procoagulant host responses to infection are intricately linked. Infectious agents and inflammatory cytokines such as tumour necrosis factor- α (TNF- α) and interleukin-1 activate coagulation by stimulating the release of tissue factor from monocytes and the endothelium. The presentation of tissue factor leads to the formation of thrombin and a fibrin clot. Inflammatory cytokines and thrombin can both impair the endogenous fibrinolytic potential by stimulating the release of plasminogen-activator inhibitor 1 (PAI-1) from platelets and the endothelium. PAI-1 is a potent inhibitor of tissue plasminogen activator, the endogenous pathway for lysing a fibrin clot. In addition, the procoagulant thrombin is capable of stimulating multiple inflammatory pathways and further suppressing the endogenous fibrinolytic system by activating thrombin-activatable fibrinolysis inhibitor (TAFI). The conversion of protein C, by thrombin bound to thrombomodulin, to the serine protease activated protein C is impaired by the inflammatory response. Endothelial injury results in decreased thrombomodulin levels. The end result of the host response to infection may be the development of diffuse endovascular injury, microvascular thrombosis, organ ischemia, multiorgan dysfunction and death. Activated protein C can intervene at multiple points during the systemic response to infection. It exerts an antithrombotic effect by inactivating factors Va and VIIIa, limiting the generation of thrombin. As a result of decreased thrombin levels, the inflammatory, procoagulant and antifibrinolytic response induced by thrombin is reduced. *In vitro* data indicate that activated protein C exerts an anti-inflammatory effect by inhibiting the production of inflammatory cytokines (TNF- α , interleukin-1 and interleukin-6) by monocytes and limiting the rolling of monocytes and neutrophils on injured endothelium by binding selectins. Activated protein C indirectly increases the fibrinolytic response by inhibiting PAI-1. Reproduced with permission from reference 16

baboon model with lethal *Escherichia coli* sepsis, infusion of rhAPC was associated with a reduced risk of death (15).

In the recently published phase III Recombinant Human Activated PROWESS trial (16), 1690 adult patients with severe sepsis were randomly assigned to receive an intravenous infusion of rhAPC 24 $\mu\text{g}/\text{kg}/\text{h}$ or placebo for 96 h. Treatment with rhAPC was associated with a 6.1% reduction in absolute mortality (210 of 850 people died in the rhAPC group versus 259 of 840 people in the placebo group) and a 19.4% reduction in the relative risk of death from any cause at 28 days after the start of infusion ($P=0.005$, number needed to treat = 16). Treatment with rhAPC significantly reduced thrombin formation, as indicated by a greater decrease in plasma D-dimer levels during the first four days after the start of infusion. Inflammatory markers were also decreased with rhAPC treatment, as indicated by decreases in IL-6 levels, demonstrating that rhAPC had effects beyond antithrombosis. There was a small increased incidence of serious bleeding associated

with rhAPC treatment compared with placebo (3.5% versus 2.0%, respectively, $P=.06$). Bleeding occurred primarily in patients with a predisposing factor to bleeding, such as trauma or recent invasive procedures. This is the first study to show a statistically significant effect of a biological product in the treatment of severe sepsis. The dosage and administration used in the study are now being applied in clinical practice, ie, intravenous administration of rhAPC 24 $\mu\text{g}/\text{kg}/\text{h}$ for 96 h.

PATIENT SELECTION

The importance of appropriate clinical management, including critical care measures, in the treatment of prospective rhAPC patients cannot be overemphasized. As in any critical care situation, treatment of the underlying condition is of primary importance. The authors strongly advocate that rhAPC be used as an adjunctive therapy in severe sepsis. It does not replace treatment of the source of infection, eradication of infectious organisms with appro-

TABLE 1
Infection criteria as defined in the Protein C Worldwide Evaluation in Severe Sepsis trial

| |
|---|
| Presence of abnormally elevated white blood cell count in normally sterile body fluid |
| Perforated viscus |
| Radiographic evidence of pneumonia associated with purulent sputum |
| Syndrome associated with a high risk of infection (eg, ascending cholangitis) |

priate antibiotic treatment and aggressive supportive care.

Treatment with rhAPC should be considered if all three of the following criteria are evident: the presence of clear indicators of a known or suspected infection (Table 1), evidence of a systemic inflammatory response, and acute organ dysfunction resulting from infection. If there is uncertainty about any of the criteria, the patient should be monitored for changes in vital signs, white blood cells (WBCs) or organ function. It should be noted that over 75% of the patients in the PROWESS trial had two or more organ dysfunctions. The authors recommend that rhAPC be considered for any patient with a proven or suspected infection serious enough to warrant intensive care unit (ICU) admission for vasopressor and ventilatory support. If shock is not present, then another organ failure is required to warrant the use of rhAPC (eg, at least two organ failures).

RECOMMENDATIONS FOR PATIENT IDENTIFICATION AND SELECTION (BASED ON PROWESS CRITERIA)

Patient identification: systemic inflammation

The ambiguity of the criteria for systemic inflammatory response syndrome (SIRS) led to the practical definition of severe sepsis for clinical treatment with rhAPC used in the PROWESS study (Tables 2,3). In particular, acute organ dysfunction associated with an infective process is required. SIRS criteria should serve as a link between the two. Tachypnea and tachycardia alone are not specific signs of an infectious process. Thus, three SIRS criteria were needed in the PROWESS study to prevent those patients with tachypnea and tachycardia from being mistakenly identified as having severe sepsis. Alterations in WBC count and temperature are more specific signs of systemic response to infection. Infection causing hypotension (which persists despite adequate volume repletion that would provide for adequate central venous pressures) identifies a specific cohort of severe sepsis patients who are prime candidates for rhAPC, because most will subsequently show evidence of other organ dysfunction, including acidosis, renal insufficiency, etc.

In some cases, the source of infection is obvious, such as patients with *S pneumoniae* and bacteremia (the commonest

TABLE 2
Definitions of sepsis*

Historical definition: Sepsis (SIRS with infection)

A systemic inflammatory response to an infection associated with, but not limited to, 2 or more (3 or more in the PROWESS trial) of the following parameters:

Core temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$ ($>100.4^{\circ}\text{F}$ or $<96.8^{\circ}\text{F}$)

Tachycardia (>90 beats per minute)

Tachypnea (respiratory rate >20 breaths/min or hyperventilation, as indicated by partial pressure of carbon dioxide in the arterial blood of <32 mmHg)

Alteration in WBC count (WBC $>12,000/\text{mm}^3$ or $<4000/\text{mm}^3$; or presence of $>10\%$ immature neutrophils)

These clinical manifestations should be part of a direct systemic response to the presence of an infectious process with an alteration from baseline in the absence of other known causes for such abnormalities

Severe sepsis (infection requiring ICU admission)

Sepsis is associated with acute organ dysfunction

Septic shock (patient requiring vasopressors)

A subset of severe sepsis, generally defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation, often results in additional organ dysfunction or hypoperfusion abnormalities (including, but not limited to lactic acidosis, oliguria or acute alteration of mental status). Patients receiving inotropic agents or vasopressors may not be hypotensive at the time perfusion abnormalities are measured

**The definition of sepsis has remained a point of controversy for many years. For the purpose of this guidance document, it is necessary to distinguish the different manifestations of sepsis encountered in the critical care population (21). ICU Intensive care unit; PROWESS Protein C Worldwide Evaluation in Severe Sepsis; SIRS Systemic inflammatory response syndrome; WBC white blood cells*

presentation in the PROWESS study), and the resulting severe sepsis associated with the infection is a clear indication for rhAPC therapy. Such cases include purpura fulminans due to meningococcemia, where administration of protein C concentrate demonstrates efficacy at not only reducing mortality but also reducing morbidity by decreasing the number of amputations required by survivors (13,17).

Patients may present with clinical signs suggestive of severe sepsis but without a clear focus of infection, such as a primary bacteremia. These patients present with fever, elevated WBC count and coagulopathy, meeting severe sepsis criteria. The authors advise treatment of such patients with rhAPC if the criteria for severe sepsis are present.

However, some patients may initially show sepsis-like symptoms that are not due to sepsis, for example, a patient with chronic obstructive pulmonary disease (COPD) who becomes hypotensive during intubation and develops purulent-looking sputum. With longer observation, one may determine that the patient does not have pneumonia but has bronchitis and that hypotension is due to hypovolemia and positive pressure ventilation. These cases should not be treated with rhAPC or, if treatment has already been initi-

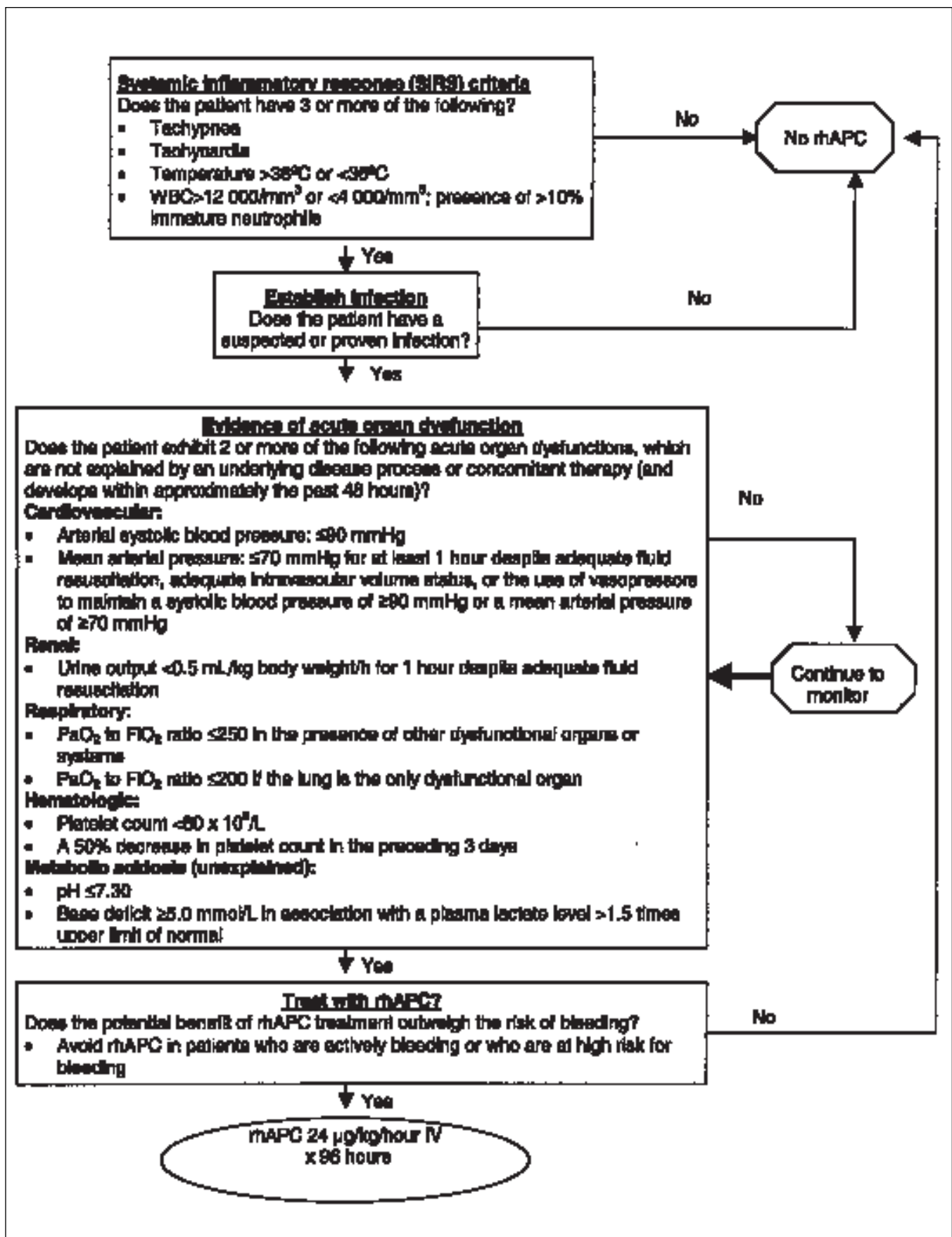


Figure 2) Appropriate patient selection for recombinant human activated protein C (rhAPC) treatment of severe sepsis. FiO₂ Fraction of inspired oxygen; PaO₂ Partial pressure of oxygen in arterial blood; SIRS Systemic inflammatory response syndrome; WBC White blood cells

TABLE 3
Practical definition of severe sepsis for clinical treatment with recombinant human activated protein C

| Generic definition of severe sepsis | |
|---|--|
| Suspected or proven infection | |
| Evidence of systemic inflammation by 3 or more SIRS criteria | |
| Sepsis-induced acute organ dysfunction or dysfunction in 2 or more organs (cardiovascular, renal, respiratory, hematological and unexplained metabolic acidosis), not explained by underlying disease process or effects of concomitant therapy | |

SIRS Systemic inflammatory response system

ated, it should be discontinued. It is therefore important that practitioners understand the cause of hypotension to initiate appropriate treatment.

The key message is to identify infection by physical examination, temperature dysregulation, changes in circulating WBC and culture results. If the clinical course is unclear, it is appropriate to wait several hours and monitor disease progression before using rhAPC. Antibiotics should be started immediately if infection is clinically suspected.

Patient identification: Acute organ dysfunction

The criteria for organ dysfunction in the PROWESS trial were necessary to identify those patients with severe sepsis (Table 4). The cut-off points, as defined in the inclusion criteria, were chosen from the best available evidence at the time, out of necessity, to provide a patient population to study that would be as uniform as possible.

One criterion was that drug therapy had to be initiated within 48 h of the onset of organ dysfunction. This rigid timing criterion was used to specifically exclude those patients likely to be experiencing organ dysfunction due to other causes (ie, it was necessary that the organ dysfunction be acute and not a result of chronic disease). Some cases were identified in which the timing of organ dysfunction precluded inclusion in the study. However, in clinical practice, it is common for patients to present within 30 to 48 h after transfer from home or other institutions. It is therefore recommended that, in cases where application of the rigid timing criterion would exclude a patient who may otherwise be considered likely to benefit from treatment with rhAPC, the timing of organ dysfunction be viewed in the context of any underlying disease. The rationale should be to exclude from consideration for treatment those patients with organ dysfunction not due to acute sepsis (eg, respiratory dysfunction in the presence of COPD). Patients presenting with organ dysfunction within a reasonable time around the 48-h mark can still be considered for treatment if the organ dysfunction is judged to be due to severe sepsis. While no data are available to directly support this recommendation, it is noteworthy that, in the PROWESS trial, rhAPC treatment administered at the 48-h limit of organ dysfunction was equally as efficacious as earlier treatment (18). Although rhAPC could be beneficial beyond 48 h if acute organ dysfunction is due to severe sepsis, in the

TABLE 4
Criteria for organ dysfunction in the PROWESS trial*

| Dysfunction | Criteria |
|--------------------------------|--|
| Cardiovascular | Arterial systolic blood pressure ≤ 90 mmHg; or Mean arterial pressure ≤ 70 mmHg for at least 1 h, despite adequate fluid resuscitation, adequate intravascular volume status, or the use of vasopressors to maintain a systolic blood pressure of 90 mmHg or a mean arterial pressure of 70 mmHg |
| Renal | Urine output < 0.5 mL/kg body weight/h for 1 h despite adequate fluid resuscitation |
| Respiratory | A ratio of PaO ₂ to FiO ₂ of ≤ 250 in the presence of other dysfunctional organs or systems; or A ratio of PaO ₂ to FiO ₂ ≤ 200 if the lung was the only dysfunctional organ |
| Hematological | A platelet count $< 80 \times 10^9/L$; or A 50% decrease in platelet count within the preceding 3 days |
| Unexplained metabolic acidosis | pH ≤ 7.30 ; or Base deficit ≥ 5.0 mmol/L in association with a plasma lactate level > 1.5 times the upper limit of the normal value for the reporting laboratory |

**In a patient whose infection or suspected infection is serious enough to warrant consideration for admission to the intensive care unit, the algorithm in this document (Figure 2) can be used to determine if recombinant human activated protein C (rhAPC) therapy is appropriate. FiO₂ Fraction of inspired oxygen; PaO₂ Partial pressure of oxygen in arterial blood; PROWESS Protein C Worldwide Evaluation in Severe Sepsis*

absence of additional data, the appropriate clinical approach should be assessed on a case by case basis.

Where the direction of the clinical course is uncertain, it may be appropriate to withhold treatment with rhAPC while continuing to assess how the patient's disease evolves, and then begin therapy if clinically indicated. If the patient shows signs of worsening organ dysfunction because of ongoing infection and meets the criteria for severe sepsis, the authors advise consideration of the use of rhAPC.

Patient selection: Risk-benefit assessment

Bleeding was the most common adverse event associated with the use of rhAPC in the PROWESS trial. The incidence of severe bleeding was 3.5% in the rhAPC group and 2.0% in the placebo group ($P=0.06$) (Table 5). As expected, this difference was noted during the four-day infusion period but was not statistically significant between both groups at 28 days. As well, blood transfusion requirements were similar for the two groups (after adjustment of duration for survival). This continues to confirm the importance of assessing and monitoring bleeding risk before, during and after treatment.

In the PROWESS trial, a serious bleeding event was defined as intracranial hemorrhage, life-threatening bleeding, bleeding classified as serious by the investigator, or

TABLE 5
Incidence of serious adverse events in the PROWESS trial

| Variable | rhAPC group (n=850) n (%) | Placebo group (n=840) n (%) | P |
|------------------------------------|---------------------------|-----------------------------|------|
| At least one serious adverse event | 106 (12.5) | 102 (12.1) | 0.84 |
| Serious bleeding event* | 30 (3.5) | 17 (2.0) | 0.06 |
| Gastrointestinal | 9 (1.1) | 9 (1.1) | |
| Intra-abdominal | 3 (0.4) | 4 (0.5) | |
| Intrathoracic | 6 (0.7) | 1 (0.1) | |
| Retroperitoneal | 4 (0.5) | 0 | |
| Intracranial | 2 (0.2) | 1 (0.1) | |
| Skin or soft tissue | 2 (0.2) | 0 | |
| Genitourinary | 2 (0.2) | 0 | |
| Source unidentified† | 2 (0.2) | 2 (0.2) | |
| Thrombotic events | 17 (2.0) | 25 (3.0) | 0.20 |

*A serious bleeding event was defined as any intracranial hemorrhage, any life-threatening bleeding, any bleeding event classified as serious by the investigator, or any bleeding that required the administration of three units of packed red cells on two consecutive days. †These patients received three units of packed red cells on two consecutive days, but had no identifiable source of bleeding. PROWESS Protein C Worldwide Evaluation in Severe Sepsis; rhAPC Recombinant human activated protein C

bleeding that required administration of three units of packed red cells on two consecutive days. Serious bleeding occurred predominantly in patients either identified to be predisposed to bleeding or associated with invasive procedures (eg, central lines, chest tubes, etc).

Patients at high risk of bleeding were excluded from the PROWESS trial and there were treatment exclusions because of concomitant antithrombotic therapies. Therefore, there may be additional unknown risks associated with the use of rhAPC in patients who do not strictly meet the PROWESS criteria. As well, there are treatment exclusions because of concomitant antithrombotic therapies. Mortality by platelet count is listed in Table 6 (18,19). Patients were enrolled only if their platelet count at baseline was greater than $30 \times 10^9/L$. However, these patients remained in the study if their counts fell below $30 \times 10^9/L$. United States Food and Drug Administration contraindications and warnings for the use of rhAPC are listed in Tables 7 and 8, respectively.

The assessment of bleeding risk is necessary in the decision to treat with rhAPC. If a possible bleeding risk is suspected, the clinician should withhold treatment with rhAPC until the true risk can be assessed.

Exclusion criteria due to possible increased bleeding risk

There may be patients who fall outside the exclusion criteria used in the PROWESS trial for whom treatment with rhAPC may be beneficial. In the following section, the PROWESS exclusion criteria are reviewed. Clinicians must keep in mind that these are guidelines only and are not

TABLE 6
PROWESS trial data with recombinant human activated protein C (rhAPC) treatment: Mortality in patients with low platelet count

| Platelet count | rhAPC n (%) | Placebo n (%) |
|---|-------------|---------------|
| <50,000 at baseline (n=40) | 4/16 (25) | 15/24 (63) |
| Minimum <50,000 baseline to study day 5 (n=113) | 12/50 (24) | 34/63 (54) |
| Minimum <30,000 baseline to study day 5 (n=34) | 5/15 (33) | 16/19 (84) |

PROWESS Protein C Worldwide Evaluation in Severe Sepsis (18,19)

meant to replace good clinical judgement or discussions with family members about the risks and benefits of such treatment. What follows is the rationale and discussion for each exclusion criterion.

Exclusion criterion: Patients receiving medications that interfere with coagulation

Patients receiving fibrinolytic therapy within three days:

Because the anticoagulant effects of fibrinolytic therapy are absent 24 h after discontinuation of such therapy, it is reasonable to use this timeframe (rather than the three days specified in the PROWESS protocol) as the period during which rhAPC therapy may be considered.

Patients receiving more than 650 mg/day acetylsalicylic acid (ASA) or other antiplatelet therapy within three days before study entry:

Although there are no data on the effects of doses of ASA less than 650 mg/day, it is important to note that as ASA affects platelet aggregation, bleeding risk may increase with the addition of an anticoagulant such as rhAPC.

Patients receiving glycoprotein IIb/IIIa antagonists within seven days before study entry:

Because the antiplatelet effects may be sufficiently attenuated earlier than seven days, it may be safe to treat with rhAPC before the seven-day window has elapsed. The antiplatelet effects of these drugs may also be reversed with platelet transfusion (for abciximab) or dialysis (for eptifibatid and tirofiban).

Patients receiving warfarin (if used within seven days before study entry and if the prothrombin time exceeded the upper limit of the normal range for the institution):

A more appropriate index of whether to administer rhAPC in a patient who has received warfarin within the previous seven days is to base this decision on the international normalized ratio (INR), regardless of time from administration of warfarin. INR should be monitored during the course of treatment with rhAPC in the event of a delayed warfarin effect.

Exclusion criterion: Platelet count of less than $30 \times 10^9/L$

The authors recommend that careful evaluation of the risks and benefits of rhAPC therapy be weighed on a case by case basis in patients with a low platelet count. Where appropri-

TABLE 7
United States Food and Drug Administration
contraindications for treatment with recombinant
human activated protein C

| |
|---|
| Active internal bleeding |
| Recent (within three months) hemorrhagic stroke |
| Recent (within two months) intracranial or intraspinal surgery, or severe head trauma requiring hospitalization |
| Trauma with increased risk of life-threatening bleeding |
| Presence of an epidural catheter |
| Intracranial neoplasm or mass lesion or evidence of cerebral herniation |

ate, rhAPC may be administered with careful monitoring for bleeding and platelet replenishment as needed.

While there may be an increased risk of a serious bleeding event such as an intracranial hemorrhage in patients treated with rhAPC with a platelet count of less than $30 \times 10^9/L$, the potential benefits of treatment may outweigh the risks. PROWESS trial results indicate that the comparative benefit is greater without an increase in mortality (Table 6). It is important to note that, despite the risk of bleeding associated with a platelet count of less than $30 \times 10^9/L$, those patients started on rhAPC treatment in the study could remain on therapy at the discretion of the investigator who could also provide transfusions and platelet infusions as needed.

Exclusion criterion: Patients requiring planned or anticipated surgery under general or spinal anesthetics

In the PROWESS trial, patients having surgery or the need for surgery (planned or anticipated) under general or spinal anesthesia were not treated with rhAPC. If treatment was initiated and surgery or an invasive procedure was subsequently required, infusion of rhAPC was stopped 1 h before any minor procedure and resumed within 1 h after the procedure. Infusion was stopped 2 h before any major surgery or invasive procedure and resumed 1 h after an invasive procedure or 12 h after surgery. It is the opinion of the authors that these guidelines should continue to be followed. A short stopping period before any percutaneous procedure or surgery is required because rhAPC has a short half-life of 13 min, and levels are virtually undetectable after 2 h.

Exclusion criterion: Evidence of active postoperative bleeding

For patients with postoperative bleeding, clinicians should exercise good clinical judgment (ie, clinical assessment in terms of resolution of bleeding, need for intervention, INR, activated partial thromboplastin time [aPTT] levels, etc) in deciding whether to use rhAPC in the management of severe sepsis. If the bleeding is not judged to pose a significant risk, infusion with rhAPC may be considered. If there is active, uncontrolled bleeding, rhAPC is contraindicated.

Exclusion criterion: History of severe head trauma requiring hospitalization; trauma considered to increase

TABLE 8
Recombinant human activated protein C (rhAPC):
United States Food and Drug Administration warnings

Certain conditions, many of which were exclusion criteria in the phase III trial, are likely to increase the risk of bleeding for therapy with rhAPC. Therefore, for patients with severe sepsis who have one or more of the following conditions, the increased bleeding risk should be carefully considered before initiating rhAPC therapy.

| |
|--|
| Concurrent therapeutic heparin (>15 units/kg/hr) |
| Platelet count $<30 \times 10^9/L$, even if the platelet count increases after transfusions |
| Prothrombin time/international normalized ratio >3.0 |
| Recent (within six weeks) gastrointestinal bleeding, unless definitive intervention has been performed |
| Recent administration (within three days) of thrombolytic therapy |
| Recent administration (within seven days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors |
| Recent administration (within seven days) of acetylsalicylic acid (>650 mg/day) or other platelet inhibitors |
| Recent (within three months) ischemic stroke |
| Intracranial arteriovenous malformation or aneurysm |
| Known bleeding diathesis, except for acute coagulopathy due to sepsis |
| Chronic liver disease |
| Any other condition in which important bleeding constitutes a significant hazard or would be difficult to manage because of location |

the risk of serious bleeding

In general, treatment with rhAPC should not be initiated in a patient with a history of recent severe head trauma requiring hospitalization due to the risk of provoking intracranial bleeding. Clinicians need to weigh this risk against the potential benefits of treatment with rhAPC. However, if a past head injury is no longer considered to be clinically significant, treatment with rhAPC could be considered. In any trauma with a potentially high level of risk of serious bleeding, the clinician should weigh this risk against the potential benefits.

Exclusion criterion: Intracranial surgery, stroke within three months, or history of intracranial arteriovenous malformation; cerebral aneurysm or mass lesions of the central nervous system

Because there is a potentially high level of risk of intracranial bleeding associated with this exclusion criterion, rhAPC is contraindicated. Tentorial herniation should also be considered an absolute contraindication.

Exclusion criterion: History of congenital bleeding diathesis

Although there are no data or clinical experience in the use of rhAPC in this population, the clinician should weigh the potential benefits and risks of treatment if appropriate coagulation factor therapy is available.

Exclusion criterion: Gastrointestinal bleeding within the previous six weeks (unless corrective surgery has been performed)

Unless corrective surgery or endoscopy has been performed, rhAPC should not be used in patients with gastrointestinal bleeding within the previous six weeks.

A number of patients were excluded from the PROWESS trial because of the increased bleeding risk associated with the coadministration of antithrombotics or anticoagulants. These criteria are also believed to be too exclusive because they may limit the use of rhAPC in a large number of patients who may otherwise benefit from therapy. For example, if a patient is receiving long term warfarin prophylaxis, administration of plasma to reverse the anticoagulant effect and a switch to subcutaneous heparin may be sufficient to allow the safe use of rhAPC. It is the opinion of the authors that the benefit of rhAPC therapy may outweigh the risks associated with the temporary stoppage of prophylactic antithrombotic or anticoagulant therapy. To date, there is no evidence that treatment with rhAPC is protective against thrombosis.

For patients receiving therapeutic warfarin, full-dose unfractionated heparin, or therapeutic-dose low-molecular-weight heparin for appropriate indications, no data exist on the potential risks and benefits of rhAPC therapy for severe sepsis compared with the risks and benefits of anticoagulant therapy for thrombosis. Therefore, the PROWESS exclusion criteria should be adhered to until such data are available.

As a final component of the risk-benefit assessment, it is important to note that some criteria for exclusion from the PROWESS trial were not based on any known safety risk, but rather on administrative reasons or reasons related to trial design. In these cases, there may be no biological or safety reasons to withhold rhAPC treatment. However, further study is advocated.

There are no known biological reasons underlying the exclusion of the following patient groups (excluded from PROWESS trial) when deciding whether treatment with rhAPC is appropriate.

- Chronic severe hepatic disease (involving varices, jaundice, encephalopathy, portal hypertension) encompasses a large population at risk of severe sepsis. Isolated liver disease alone, even if severe, need not be a reason for withholding rhAPC if treatment is otherwise indicated and if the associated bleeding diathesis is monitored and can be controlled by appropriate coagulation factor replacement. However, rhAPC therapy would be appropriately withheld in patients with both severe liver disease and a history of bleeding or recent hemorrhage (eg, known variceal disease).
- The study of paediatric administration of rhAPC has been completed (20) and demonstrates the possible benefit of rhAPC in children younger than 18 years of age, such as those with sepsis-induced

disseminated intravascular coagulation (DIC) (eg, meningococemia).

- Weight exclusion was included to ensure homogeneous dosing in the trial. In patients weighing more than 135 kg, the same $\mu\text{g}/\text{kg}/\text{h}$ dose should be used because evidence indicates a linear relationship between clearance and body weight.

Also excluded were patients with a history of bone marrow, lung, liver, pancreas or small bowel transplantation. The use of rhAPC has not been assessed in these patient populations; however, strict application of this limitation, necessary in the context of the trial, would preclude the use of rhAPC in some patients who may potentially benefit from the drug. In the absence of further data, a clear recommendation cannot be made, but potential risks and benefits must be considered in each individual case by the clinician.

MANAGEMENT OF BLEEDING RISK

General management

It is important to monitor the INR, aPTT and platelet count closely in all patients with severe sepsis, particularly in those receiving rhAPC treatment. There are no specific indications regarding levels of these parameters other than clinical assessment. rhAPC has a minimal effect on prothrombin time; however, at the recommended dose, rhAPC may moderately (but variably) prolong aPTT. Routine monitoring of aPTT is conducted only as needed to assess the patient's bleeding risk, not the rhAPC therapy. The half-life of rhAPC is 13 min in blood, and levels are almost undetectable after 2 h. Endogenous proteases also break down APC in a blood sample over 30 minutes. Therefore, a minimum 30-min interval between blood collection and performance of the aPTT assay is recommended to minimize the potential effect of rhAPC on aPTT assay. Because a prolongation of aPTT may be due to underlying coagulopathy or concurrent medications, delaying the assay run will eliminate the pharmacodynamic effect of rhAPC, although the clinical significance of this effect is unknown at this time.

Elevated INR or aPTT are not exclusion criteria for the use of rhAPC but require close monitoring. As a general rule, patients with coagulation abnormalities not due to rhAPC should be managed according to standard practice, which may include plasma and/or platelets as required and replacement of coagulation factors as indicated. There is also no evidence that the dosage calculation of rhAPC should be altered for any reason, including aPTT levels.

DIC

DIC is not a reason to withhold rhAPC therapy. In patients with DIC, the underlying coagulopathy must be appropriately treated. An effective treatment for DIC appears to be rhAPC. If necessary, plasma and platelets should be administered to control the risk of bleeding and any necessary coagulation factors should be replenished. For example, if a patient with DIC who is being treated with rhAPC infusion

TABLE 9
Invasive procedures during the recombinant human activated protein C (rhAPC) infusion, as per the PROWESS trial

| Procedure | Recommended action |
|---|--|
| Central venous catheter Tracheostomy change Arterial catheter Endotracheal tube change | Hold rhAPC for 1 h before and restart immediately after |
| Chest tube Sinus puncture Thoracentesis Lumbar puncture Tracheostomy | Hold rhAPC for 2 h before and 1 h after |
| Epidural catheter | Insertion: Hold rhAPC for 2 h before and do not restart Removal: Hold rhAPC for 2 h before and 12 h after |
| Major surgery | Hold rhAPC for 2 h before and 12 h after |

PROWESS Protein C Worldwide Evaluation in Severe Sepsis

develops mild to moderate upper-gastrointestinal bleeding, a reasonable response would be to stop the infusion, take steps to stop the bleeding (which might include transfusion of plasma and platelets and, possibly, upper-gastrointestinal endoscopy), and then reassess whether restarting rhAPC is in the patient's best interest. Repletion of needed coagulation factors in patients who are at risk of bleeding is appropriate patient management during the concurrent administration of rhAPC.

Dialysis

Dialysis patients frequently take heparin. If a patient is receiving over 15,000 units/day of heparin (greater than the prophylactic dose), rhAPC should be discontinued for the period of dialysis. In patients receiving only prophylactic doses of heparin and in whom rhAPC therapy is continued throughout dialysis, clearance of the drug does not appear to be affected because the molecular weight of rhAPC (64,000 Da) precludes its movement across the membrane. At this time, the concomitant use of heparin with rhAPC for the treatment of a dialysis catheter-related thrombus has not been evaluated and cannot be recommended.

Surgery

If a surgical procedure becomes necessary during rhAPC infusion, a general recommendation is to stop the infusion for 2 h before the surgery. However, during the PROWESS trial, several patients underwent urgent surgical procedures immediately after the infusion was stopped, and did not experience untoward complications. Treatment with rhAPC can be restarted 12 h after major surgery and when there is no evidence of ongoing bleeding. Other procedures that may require discontinuation of rhAPC are listed in Table 9.

SUMMARY

rhAPC is recommended for the treatment of severe sepsis (sepsis associated with organ dysfunction). Therapy with rhAPC is intended to complement adequate, supportive

critical care and treatment of the underlying infectious source. Bleeding may be a factor that can influence patient selection; however, the risk may be effectively managed with careful monitoring and risk-benefit assessment. Although several patient populations were excluded from the PROWESS trial, this does not mean that all such patients are not candidates for rhAPC therapy. On the other hand, the data do not demonstrate a treatment benefit in patients with a low risk of death. Readers are encouraged to review the PROWESS trial and to assess the risks and benefits for each of the trial exclusion criteria for themselves. Because acute physiology and chronic health evaluation (APACHE II) scoring is not routinely used at the bedside, we recommend two organ failures and a deteriorating clinical course as clinical markers of severe illness that would merit consideration for rhAPC therapy. Good clinical judgement and careful assessment of the relevant parameters should be used in identifying prospective patients who are likely to benefit the most from this agent.

Although many of the recommendations and approaches suggested within this document are considered to be more stringent than the criteria defined within the PROWESS trial (eg, two organ failures), the authors continue to advise clinicians to exercise their best clinical judgement in weighing the risks and benefits of rhAPC therapy on a case by case basis.

The following are the authors' recommendations for the use of rhAPC in the treatment of patients with severe sepsis:

- Treatment with rhAPC can be used as adjunctive therapy. It does not replace timely antibiotic treatment of the source of infection, eradication of infectious organisms, and aggressive supportive care, but rather, complements it.
- The following should be assessed before administering rhAPC:
 - signs of systemic inflammation in response to infection (SIRS criteria);

- the presence of three or more of the following criteria: abnormal temperature, tachycardia, tachypnea and abnormal WBC count; and
- evidence of acute organ dysfunction due to infection.
- The use of rhAPC may be indicated where severe sepsis is associated with two or more organ dysfunctions and/or shock. A typical patient is one who requires ICU admission and vasopressors plus ventilatory support. Patients with single organ dysfunction should be monitored, and if there is evidence of progressive clinical deterioration, treatment with rhAPC should be considered.
- Two organ dysfunctions reflect a group of patients more seriously ill than may have been entered into the PROWESS study in which a single organ dysfunction was required.
- Hypotensive patients are prime candidates for therapy with rhAPC when persistent hypotension does not respond to fluid replacement and is caused by infection.
- Risk of bleeding: Treatment with rhAPC is associated with a small increased incidence of serious bleeding, according to available published data. Treatment with rhAPC should be withheld in patients who are actively bleeding or at high risk for bleeding.
- In the absence of contraindication, rhAPC should be considered in all cases of purpura fulminans associated with meningococemia and necrotizing soft tissue infections (as long as adequate surgery has been performed and the criteria for severe sepsis are met). Considering that these conditions involve severe coagulopathy and a high mortality rate, the risks versus benefits of treatment with rhAPC should be weighed.
- In patients with a low platelet count, elevated INR or elevated aPTT, the decision to treat with rhAPC should be based on the clinical situation and careful assessment of risk of bleeding versus benefits of treatment.
- INR, aPTT and platelet count should be monitored at least daily during rhAPC therapy. Note that rhAPC has a minimal effect on prothrombin time; however, at the recommended dose, rhAPC may moderately (but variably) prolong aPTT.
- Repletion of needed coagulation factors in patients at risk of bleeding is appropriate patient management during the concurrent administration of rhAPC.
- Treatment with rhAPC infusion should be stopped

before surgery or procedures associated with bleeding risk. Refer to “Management of bleeding risk” for specific recommendations.

FREQUENTLY ASKED QUESTIONS AND CLINICAL CHALLENGES

Q: Can treatment with rhAPC be restarted if previously discontinued?

A: In the PROWESS trial, no patient developed neutralizing antibodies to rhAPC. No adverse effects would be expected from restarting rhAPC therapy if previously discontinued. In addition, no concerns related to efficacy currently exist under these circumstances.

Q: Is it necessary to monitor protein C levels in patients before treatment with rhAPC?

A: The efficacy of rhAPC was demonstrated regardless of whether or not patients had a deficiency in protein C at baseline. These findings suggest that measurement of protein C levels is not necessary to define patients who will benefit from treatment with rhAPC.

Q: What are the critical parameters regarding aPTT measurements in rhAPC treatment?

A: rhAPC is inactivated by endogenous serum proteases. Therefore, it is recommended that aPTT measurements in blood samples be delayed for 30 min after blood collection to allow for full inactivation of rhAPC.

Q: What should I do with the rhAPC infusion if the patient exhibits uncontrolled bleeding?

A: If bleeding is considered to be clinically significant, stop the infusion, manage the bleeding and then reassess.

Q: How do I manage abnormal coagulation factors?

A: Approach the evaluation of coagulopathy in sepsis as outlined under “Management of bleeding risk”.

Q: Can prophylactic heparin be given with rhAPC?

A: Yes; up to 15,000 units per day.

Q: Can systemic heparinization for conditions such as deep vein thrombosis be given with rhAPC?

A: No. Patients who need full heparinization should not receive rhAPC. Treatment with rhAPC should be stopped if full dose heparinization is necessary for clinical purposes.

Q: What if I check coagulation parameters 4 h into infusion and they are abnormal?

A: One option is to stop the infusion; however, it is also reasonable to continue the infusion because the coagulopathy is likely due to sepsis.

Q: When must infusion of rhAPC be unquestionably stopped?

A: Infusion of rhAPC therapy should be unquestionably stopped when there is uncontrolled or life-threatening bleeding. The patient should be stabilized, and it should be determined if there were reversible factors contributing to the bleed (eg, aPTT, thrombocytopenia). It is recommended that infusion be stopped if nothing appears to be correctable.

Q: What are some common issues about treatment with rhAPC?

TABLE 10
Common concerns about treatment with recombinant human activated protein C (rhAPC)

| Problem | Recommendation |
|--|--|
| Potential bleeding risk | Wait until full risk is known before administration of rhAPC; discontinue if infusion has been started |
| Concomitant anticoagulant therapy | Modify anticoagulant therapy (eg, subcutaneous heparin), if possible |
| Timing issues | If other criteria are met with continuing organ functional deterioration, use rhAPC if close to the 48-h window from onset of organ failure |
| Suspected infection with no clear source | In combination with at least 3 SIRS criteria, there should be a strong clinical suspicion (eg, history, physical examination, other data) of an infectious etiology and evidence of two or more acute organ dysfunctions |

SIRS Systemic inflammatory response syndrome

A: Common concerns about treatment with rhAPC are listed in Table 10.

Q: Is rhAPC effective in patients with a low APACHE II score?

A: One of the consequences of the PROWESS study being stopped prematurely due to the beneficial effect of rhAPC compared with placebo was a decreased ability to form conclusions regarding benefit in small patient subgroups. Therefore, definite conclusions about efficacy in these subgroups can only be made in patients with APACHE II scores of greater than 25.

Based on this uncertainty, the authors recommend that severely ill patients with high APACHE II scores (for those who use this as part of their patient management) and/or those who have two or more organ failures would be appropriate for rhAPC treatment. Patients who do not meet this

criterion should be monitored. If their clinical course is deteriorating, rhAPC should be considered. If patients are stable or improving with ICU/infection management alone, such patients would likely not benefit from the addition of rhAPC. Note that in subgroup analysis, patients with higher APACHE II scores had greater absolute mortality reductions. Clinical evaluation of organ failure is a better marker.

ACKNOWLEDGEMENTS: Funding for this project was provided by Eli Lilly Canada Inc, whose representatives participated in the discussions. The sponsor convened a meeting of Canadian intensivists and infectious disease experts to develop a guidance document for the use of recombinant human activated protein C (rhAPC). This document represents the consensus opinion of the independent expert participants and does not necessarily reflect the opinion of the sponsor.

REFERENCES

- Linde-Zwirble WT, Angus DC, Carcillo J, Lidicker J, Clermont G, Pinsky MR. Age-specific incidence and outcome of sepsis in the US. *Crit Care Med* 1999;27(Suppl 1):A33.3. (Abst)
- Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.
- Bone RC, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest* 1997;112:235-43.
- Vervloet MG, Thijs LG, Hack CE. Derangements of coagulation and fibrinolysis in critically ill patients with sepsis and septic shock. *Semin Thromb Hemost* 1998;24:33-44.
- Levi M, Ten Cate H. Disseminated intravascular coagulation. *N Engl J Med* 1999;341:586-92.
- Iba T, Kidokoro A, Yagi Y. The role of the endothelium in changes in procoagulant activity in sepsis. *J Am Coll Surg* 1998;187:321-9.
- Nesheim M, Wang W, Boffa M, Nagashima M, Morser J, Bajzar L. Thrombin, thrombomodulin and TAFI in the molecular link between coagulation and fibrinolysis. *Thromb Haemost* 1997;78:386-91.
- Esmon CT. Inflammation and thrombosis: Mutual regulation by protein C. *Immunologist* 1998;6:84-9.
- Bajzar L, Nesheim ME, Tracy PB. The profibrinolytic effect of activated protein C in clots formed from plasma is TAFI-dependent. *Blood* 1996;88:2093-100.
- Fourrier F, Chopin C, Goudemand J, et al. Septic shock, multiple organ failure, and disseminated intravascular coagulation: compared patterns of antithrombin III, protein C, and protein S deficiencies. *Chest* 1992;101:816-23.
- Lorente JA, García-Frade LJ, Landín L, et al. Time course of hemostatic abnormalities in sepsis and its relation to outcome. *Chest* 1993;103:1536-42.
- Boldt J, Papsdorf M, Rothe A, Kumle B, Piper S. Changes of the hemostatic network in critically ill patients – is there a difference between sepsis, trauma, and neurosurgery patients? *Crit Care Med* 2000;28:445-50.
- Powars D, Larsen R, Johnson J, et al. Epidemic meningococemia and purpura fulminans with induced protein C deficiency. *Clin Infect Dis* 1993;17:254-61.
- Hartman DL, Bernard GR, Rosenfeld BA, Helterbrand JD, Yan SB, Fisher CJ. Recombinant human activated protein C (rhAPC) improves coagulation abnormalities associated with severe sepsis. *Intensive Care Med* 1998;24(Suppl 1):S229. (Abst)
- Taylor FB Jr, Chang A, Esmon CT, D'Angelo A, Vigano-D'Angelo S, Blick KE. Protein C prevents the coagulopathic and lethal effects of *Escherichia coli* infusion in the baboon. *J Clin Invest* 1987;79:918-25.
- Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699-709.
- Smith OP, White B, Vaughan D, et al. Use of protein-C concentrate, heparin, and haemodiafiltration in meningococcus-induced purpura fulminans. *Lancet* 1997;350:1590-3.
- United States Food and Drug Administration Briefing Document: Anti-Infective Advisory Committee. Drotrecogin alfa (activated) [Recombinant human activated protein C (rhAPC)]. Xigris. BLA#125029/0. <http://www.fda.gov/ohrms/dockets/ac/01/briefing/3797b1_02_FDA briefing.pdf>. Version current at March 26, 2002.
- Data on file, Eli Lilly Inc, Toronto, Ontario, 2001.
- Giroir BP. Pharmacodynamics, pharmacokinetics and safety of drotrecogin alfa (activated) in children with severe sepsis. The 31st Critical Care Congress. San Diego: January 27, 2002.
- Bone RC, Balk RA, Cerra FB, et al, for the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644-55.

ERRATA

In the Original Article “Guidance on patient identification and administration of recombinant human activated protein C for the treatment of severe sepsis” published in the November/December issue of *The Canadian Journal of Infectious Diseases* on pages 361 to 372 Figure 2 on page 365 was printed as an incomplete figure. Please see the next page for the complete figure.

ERRATA

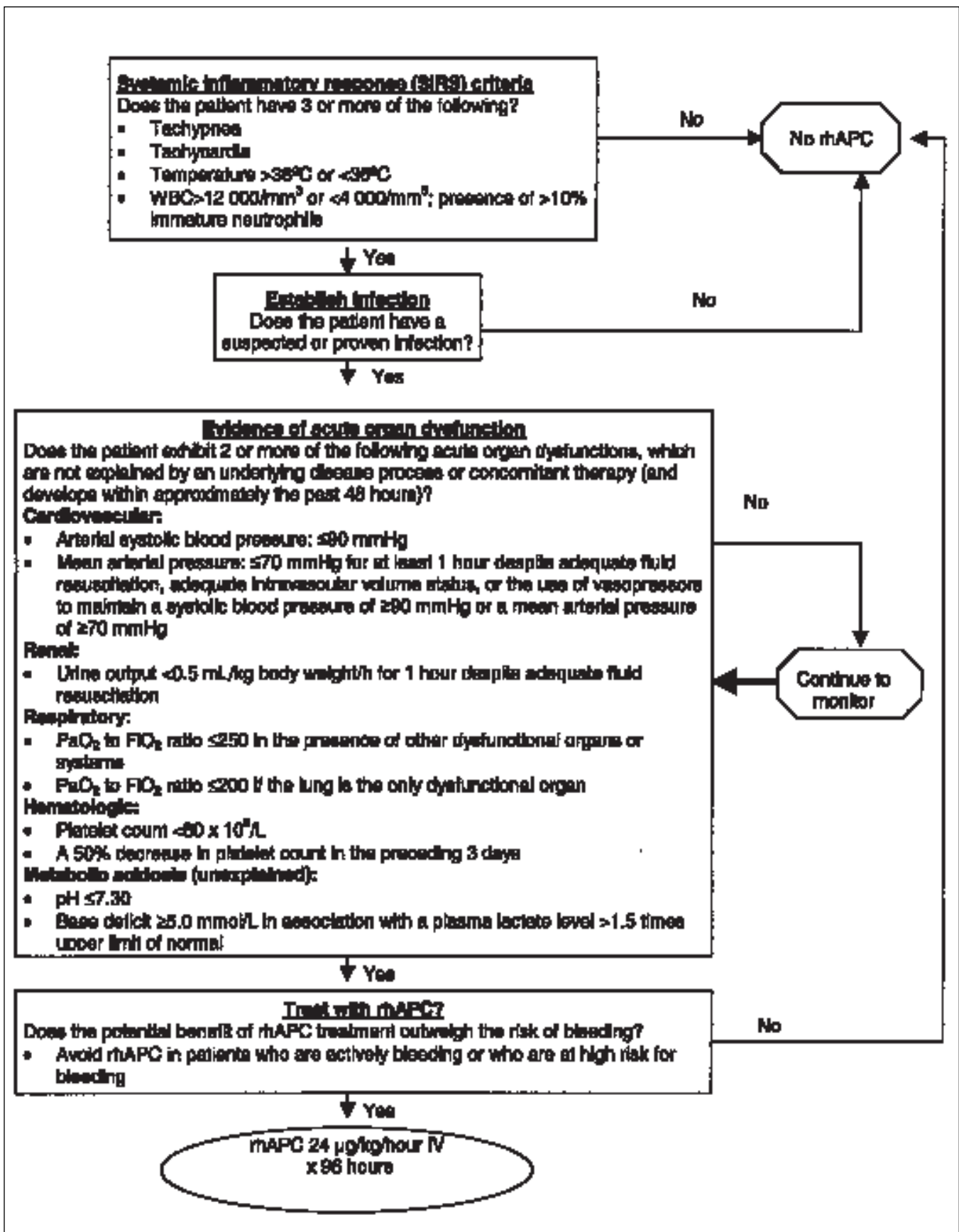


Figure 2) Appropriate patient selection for recombinant human activated protein C (rhAPC) treatment of severe sepsis. FiO₂ Fraction of inspired oxygen; PaO₂ Partial pressure of oxygen in arterial blood; SIRS Systemic inflammatory response syndrome; WBC White blood cells