Abstract

In November 2001, drotrecogin alfa (activated) was approved by the US Food and Drug Administration; in August 2002 it was approved by the European Medicines Agency. Since the approval of drotrecogin alfa (activated), however, critical care physicians have been faced with several challenges, namely its costs, selection of patients who are more likely to benefit from it, and the decision regarding when to start drotrecogin alfa (activated) treatment. There are also operational issues such as how to manage the infusion to deliver an effective treatment while minimizing the risk for bleeding, particularly in patients with deranged clotting, at around the time of surgery or during renal replacement therapy. While addressing these issues, this review remains practical but evidence based as much as possible.

Introduction

Severe sepsis and septic shock respectively account for about 37% and 15% of patients admitted to intensive care units (ICUs) in Europe [1]. They are also the leading causes of death [2], with 27% and 47% ICU mortality, and 36% and 57% hospital mortality, respectively [1]. Data from the Intensive Care National Audit and Research Centre in England, Wales, and Northern Ireland show that the number of patients with severe sepsis admitted to the ICU is increasing over time [3], which is responsible for an increase in the absolute number of deaths, despite an improved standard of care and reduced hospital mortality.

The mechanisms that lead to organ dysfunction in severe sepsis are complex. Deranged procoagulant and proinflammatory host responses to infection can lead to endothelial damage, impairment of the microcirculation and tissue hypoperfusion [4,5]. In this intricate system, activated protein C plays a key role in preserving and restoring tissue perfusion through its potent antithrombotic, profibrinolytic, and anti-inflammatory properties [6-8].

During systemic sepsis, however, inflammation and endothelial dysfunction impair the conversion of protein C (PC) to its activated protein C form. Hence, almost 88% of patients with sepsis have low levels of PC (< 80% of normal), and 40% have levels of PC that are severely reduced (<40% of normal) [9]. This can lead to excessive inflammation, formation of microthrombi and multiple organ failure, with an associated poor outcome [6,7,10,11].

Drug approval and guidelines

In 2001 the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial was reported [9]. It found that a 96-hour intravenous infusion (24 μg/kg per hour) of drotrecogin alfa (activated; DrotAA), a recombinant human activated protein C (Xigris®; Eli Lilly and Company, Indianapolis, IN, USA), caused a relative risk reduction (RRR) for mortality at 28 days of 19.4% (95% confidence interval [CI] 6.6% to 30.5%). The absolute risk reduction (ARR) for mortality was 6.1% (95% CI 1.9% to 10.4%) and the number needed to treat (NNT) to save one additional life was 16 (95% CI 52.6 to 9.6) [9]. In November 2001 DrotAA was approved by the US Food and Drug Administration (FDA); in August 2002 it was approved by the European Medicines Agency (EMEA). Both organizations licensed DrotAA for use in patients with severe sepsis at high risk for death, but they differed in their definition of risk for death. High risk for death was defined by the US label as an acute Physiology and Chronic Health Evaluation (APACHE) II
score of 25 or more (as indicated by subgroup data from PROWESS) and by the European Union label as the presence of multiple organ dysfunction. The European Union decision was based on the greater survival benefit observed in patients with two or more organ dysfunctions who were treated with DrotAA (RRR 22% and ARR 7.4%; NNT 13.5), with a bleeding risk similar to that in the overall study population [12,13].

The use of DrotAA has also been endorsed by international societies and included in the Surviving Sepsis Campaign (SSC) guidelines. In the UK, DrotAA is recommended by the National Institute for Clinical Excellence for use in adults with multiple organ failure secondary to severe sepsis who are provided with optimum intensive care support [14].

A condition of the initial approval of DrotAA by the FDA in 2001 was that additional data were to be provided and further trials conducted. Specifically, data from the long-term follow up of survivors from the PROWESS study were to be submitted [15]. Safety and efficacy of DrotAA were to be evaluated in adult patients at lower risk for death (the Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis [ADDRESS] trial [16]). Safety and efficacy of DrotAA in paediatric patients with severe sepsis were to be evaluated (the REsearching severe Sepsis and Organ dysfunction in children: a Global perspective [RESOLVE] trial [17]). Finally, a study was to be conducted to determine whether low-dose heparin has an effect on mortality in adult patients who are receiving DrotAA (the Xigris and Prophylactic HeparIn Evaluation in Severe Sepsis [XPRESS] trial [18]).

In February 2007, following discussions with the EMEA and because of ongoing equipoise among some critical care physicians, Lilly announced that they would be conducting a further trial of DrotAA in the currently indicated population. This new trial (known as PROWESS Shock) is planned to start in 2008.

Since the approval of DrotAA, however, critical care physicians have been faced with several challenges: its costs, the selection of patients who are more likely to benefit from it, and the decision on when to start DrotAA. There are also operational issues on how to manage the infusion in order to deliver an effective treatment while minimizing the risk for bleeding, particularly in patients with deranged clotting, at around the time of surgery or during renal replacement therapy.

Use of drotrecogin alfa (activated) in adults

Does drotrecogin alfa (activated) increase survival in severe sepsis?

The PROWESS trial and subsequent registries in different nations have documented a consistent reduction in mortality in patients with severe sepsis when treated with DrotAA (Table 1). Following publication of the PROWESS trial findings [9], the open-label Extended Evaluation of Recombinant Human Activated Protein C (ENHANCE) trial [19] showed a mortality rate similar to that in PROWESS, adding further support to the findings of the original controlled trial. Descriptive analyses of national registries have also confirmed that the results of the PROWESS trial are robust.

According to the findings of the global Promoting Global Research Excellence in Severe Sepsis database of 12,492 patients with severe sepsis from 37 countries [20], the adjusted odds ratio (OR) for hospital mortality associated with DrotAA was 0.75 (95% CI 0.63 to 0.89; P = 0.002), which is similar to that observed in the PROWESS trial (OR 0.8, 95% CI 0.69 to 0.94) [9]. Similarly, in the UK, Intensive Care National Audit and Research Centre data indicate that the relative risk for death associated with DrotAA was between 0.75 (95% CI 0.68 to 0.83) and 0.85 (95% CI 0.78 to 0.93) [21]. These studies also demonstrate a greater treatment effect for patients with three or more organs in failure, with an ARR for dying of up to 17% [20,21].

These data are consistent with the clinical experiences of other national registries. Data from a Polish registry showed that patients treated with DrotAA with a mean of 3.7 organs in failure had an ARR for death of 17.3% (38.9% versus 56.2%), giving an NNT of 6 [22]. In the group of patients with APACHE II scores of 25 or more, the absolute mortality risk was reduced by 13% [22]. Likewise, a Belgian registry suggested that DrotAA reduced the odds of death by 39% (OR 0.61, 95% CI 0.40 to 0.92), with an adjusted ARR of 12.8% (expected versus observed mortality of 63.5% versus 50.7%) [23,24]. Data from an Italian pharmaco-surveillance registry showed an 8.4% ARR in patients treated with DrotAA (46.4% versus 54.9%; P = 0.0004), but these data must be interpreted with caution because the untreated group included older patients and a greater percentage of patients in septic shock (66.8% versus 77.1%; P < 0.0001) who were therefore at greater risk for death [25].

Also favourable are the long-term outcome data. Follow-up data from the PROWESS study showed that hospital survival is greater with DrotAA (70.3% versus 65.1% for placebo) [15], with no extra ICU resource use apart from the DrotAA acquisition cost [26]. Patients with more severe disease and an APACHE II score of 25 or more had a longer median survival time (379 days), and an additional 11% of patients in the DrotAA group were alive at 1 year [15].

Which patients should be considered for treatment with drotrecogin alfa (activated)?

Faced with the decision of whom to treat with DrotAA, intensivists should consider in which patients is treatment with DrotAA indicated, and in which patients is the greatest benefit in terms of both mortality and cost-effectiveness likely to be realized.
Most of the trials have used inclusion and exclusion criteria similar to those in the PROWESS trial [9]. In our experience, in which we have treated more than 300 patients with DrotAA, the exclusion criteria most frequently encountered are severe chronic illness, high bleeding risk, advanced cancer, excluded concomitant medication, expected survival under 24 hours, and severe thrombocytopenia (platelet count < 30,000/mm³) [27].

It is clear that the key to appropriate use of DrotAA lies in the assessment of risk for death. However, there is still no consensus on a good operational definition of ‘high risk’ in patients with severe sepsis. In the USA DrotAA is recommended in patients ‘at high risk of death, for example, those with an APACHE II score of = 25’, whereas in the European Union DrotAA is indicated in the presence of multiple organ dysfunction, irrespective of pretreatment APACHE II score. The recommendations of the SSC guidelines are based on APACHE II score, organ dysfunction, the presence of septic shock and sepsis-induced acute respiratory distress syndrome, but the SSC also acknowledges the lack of a clear definition of high risk and emphasizes the importance of clinical judgement in guiding timely treatment with DrotAA [4].

Using the APACHE II score to select patients for treatment with DrotAA has several limitations. Initially, this score was developed for use in populations, not to inform decisions in individual patients. Moreover, the APACHE II score in the PROWESS trial was calculated based on data obtained within the 24 hours before study randomization, not during the first 24 hours in the ICU. This renders the APACHE score problematic in assisting patient selection because physiological parameters change continuously and are modified by treatment. The APACHE II score may change but not necessarily the severity of the underlying process [7]. In spite of this, an APACHE score above 25 did appear to identify a group of patients who were highly likely to experience a long-term survival benefit [15].

Results from the ADDRESS trial [16], which was conducted in patients at ‘lower risk of death’, confirmed that the original decisions of the FDA and EMEA may have been correct in terms of the wording of their licences. In this trial, enrolment was terminated early because interim analysis revealed a low likelihood that DrotAA would significantly reduce the 28-day mortality rate. Of the 2,613 patients, including 1,297 in the placebo group and 1,316 in the DrotAA group, both groups had similar 28-day mortality (17.0% with placebo versus 18.5% with DrotAA; \( P = 0.34 \)) and in-hospital mortality (20.5% versus 20.6%; \( P = 0.98 \)).

### Static or dynamic assessment of risk for death

In patients with severe sepsis, the number of organs in failure is frequently used for prognostication at the bedside. In addition, multiple scoring systems (for instance, the Sequential Organ Failure Assessment [SOFA] score and the Multiple Organ Dysfunction Score) were developed to help clinicians to summarize organ dysfunction and to predict risk for death [28,29]. Although the degree of organ dysfunction at baseline, calculated for example using a SOFA score, is highly predictive of 28-day mortality, it appears probable that a single assessment in time is inferior to assessment of dynamic changes (for instance, delta SOFA) [30,31]. Using such a dynamic measurement over time more closely reflects the patient’s response to therapeutic interventions [32], in that improvement in cardiovascular, renal, or respiratory function from baseline to day 1 is significantly related to improved survival. For example, based on static baseline measurements, the mortality rate in patients not receiving vasopressors decreased by 6% if they remained on no vasopressors; it increased by 11% and 32% if patients required a low or high dose of vasopressors, respectively, at day 1 [32]. The effects of DrotAA on dynamic changes in vasopressor use and SOFA score during the first 24 hours of treatment with DrotAA are currently being tested in a phase IV open label trial, which is expected to complete recruitment in December 2007 (http://clinicaltrials.gov/ct2/show/NCT00279214?term=drotrecogin&rank=4).

As well as using baseline organ dysfunction to predict mortality, dynamic assessment of the plasma level of PC concentration has been shown to predict mortality in

### Table 1: Effects of drotrecogin on mortality in National Registry data

| Registry/Trial | Country     | Patients treated with DrotAA (% of cases) | ARR  | OR (95% CI) |
|---------------|-------------|------------------------------------------|------|-------------|
| PROWESS      | International | 1,690                                    | 6.1% | 0.8 (0.69 to 0.94) |
|               | UK [21]     | 1,245 (6.3%)                             | 0.75 (0.68 to 0.83) |
|               | Poland [22] | 302 (9.3%)                               | 17.3%     |
| PROGRESS     | International [20] | 882 (7%)                       | 0.75 (0.63 to 0.9) |
|               | Belgium [24] | 430                                      | 12.8% | 0.61 (0.40 to 0.92) |

ARR, absolute risk reduction; CI, confidence interval; DrotAA, drotrecogin alfa (activated); OR, odds ratio; PROGRESS, Promoting Global Research Excellence in Severe Sepsis; PROWESS, Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis.
severe sepsis [33]. In particular, having low PC levels (<40% of normal) carries an OR for death of 2.75. The OR ratio improved to 0.43 if levels rose above 40% of normal on day 1. Conversely, for patients with PC above 40%, a decrease by more than 10% increased the risk for death by 1.78 [33]. Perhaps these changes could be used not only prognostically but also to guide treatment in terms of the dose and duration of DrotAA therapy. A phase II clinical trial (RESPOND trial [Research Evaluating Serial Protein C levels in severe sepsis patients ON Drotrecogin alfa (activated)]; NCT00386425; http://clinicaltrials.gov/ct2/show/NCT00386425?term=drotrecogin&rank=6) is evaluating the impact of different doses and duration of treatment with DrotAA on the change of plasma levels of PC using serial measurements of PC in patients with severe sepsis.

Effects of drotrecogin alfa (activated) in different clinical subgroups

Demographics

Several subgroup analyses of the PROWESS trial have been performed based on clinical and biochemically relevant baseline variables. These analyses have found that the relative risk reductions in these subgroups were not statistically different from those in the overall population and allow substantial confidence that the overall study result was robust. In particular, the subgroup analysis of elderly patients (>75 years) who were treated with DrotAA demonstrated ARRs in 28-day mortality of 15.5%, with a relative risk of 0.68 (95% CI 0.54 to 0.87) and a NNT of 6 to 7, and similar rates of serious adverse events [34].

Community-acquired pneumonia

A subgroup analysis was conducted in patients with severe sepsis caused by community-acquired pneumonia (CAP), with a CURB-65 (confusion, urea, respiratory rate, blood pressure, age >65 years) score of above 3, who were treated with DrotAA [35]. It demonstrated a RRR in mortality of 28% at 28 days, and of 14% at 90 days. The survival benefit was most pronounced in severe CAP patients with Streptococcus pneumoniae infection and in CAP patients at high risk for death, as indicated by an APACHE II score above 25, Pneumonia Severity Index score above 4, or CURB-65 score above 3.

Purpura fulminans meningitis and meningococcal disease

A small proportion (4.6%) of patients from the PROWESS and ENHANCE trials and a compassionate use programme (study EVAS) had purpura fulminans, meningitis, or meningococcal disease. Overall, these patients exhibited an ARR of 6.5%, similar to that in the PROWESS study. When analyzed in isolation, however, the ARRs of death after DrotAA were 16.7% for meningococcal disease, 7.1% for meningitis, and 4% for purpura fulminans [36]. The rate of severe bleeding events was similar to that in the rest of the population, but there was a higher rate of intracranial haemorrhage (4.3% versus 1%), with the highest rate being recorded for meningitis (5.7%). This may simply reflect the high risk for developing intracranial haemorrhage in this population, independent of DrotAA. It is noteworthy that despite the higher total number of bleeding events, the number of fatal bleeding events was similar to that in the rest of the population, both during the infusion period (0.6% versus 0.4%) and over the 28-day period (0.6% versus 0.8%) [36].

Surgical patients

Of patients included in the PROWESS population, 28% had undergone surgery within the 30-day period prior to study entry. Overall, these patients exhibited a smaller mortality benefit of 3.2%; however, the subpopulation of patients who underwent an abdominal operation had an overall 9.1% ARR and 30% RRR (relative risk 0.7, 95% CI 0.48 to 1.03). When patients with an APACHE II score of 25 or greater were considered, the ARR was even higher, at 18.2%, and the RRR was 40% (relative risk 0.6, 95% CI 0.36 to 1.0) [37].

The rates of serious bleeding events were not dissimilar from those in nonsurgical patients (3.1% versus 2.1% during the infusion period, and 3.5% versus 3.5% during the 28-day period) [37]. Furthermore, data from INDEPTH (International Integrated Database for the Evaluation of Severe Sepsis and DrotAA Therapy) [38] showed a significant reduction in mortality (OR 0.66, 95% CI 0.45 to 0.97) in surgical patients with severe sepsis and a high risk for death. Surgical patients at a lower risk for death do not appear to benefit from therapy with DrotAA.

Pancreatitis

Acute severe pancreatitis leads to a marked systemic inflammatory response; however, the role played by infection during the acute phase of the disease is unclear. Patients with pancreatitis admitted to the ICU have mortality rates in the range of 30% to 50% and a mean hospital length of stay in excess of 1 month [39]. One of the complications is the occurrence of a catastrophic retroperitoneal haemorrhage. For this reason, patients with acute pancreatitis but without evidence of infection were excluded from the PROWESS trial. However, 62 patients (3.7% of the patients) with pancreatitis and severe sepsis were enrolled in the trial. In these patients, mortality was 24% in the placebo arm and 15% in those receiving DrotAA (ARR 9% and NNT 11).

Experience outside clinical trials also supports careful use of DrotAA in the context of infection and pancreatitis [40]. The International Consensus Conference on severe acute pancreatitis recommended that use of DrotAA be considered together with conventional treatment in patients with severe acute pancreatitis and severe sepsis, bearing in mind the theoretical but unproven concern of retroperitoneal haemorrhage [39,41].

Disseminated intravascular coagulation

Although a baseline thrombocytopenia (platelet count <30,000/mm³) was an exclusion criterion in the PROWESS
trial, subsequent analyses of the PROWESS trial demonstrated an increased survival benefit in patients with overt disseminated intravascular coagulation (DIC) treated with DrotAA as compared with patients without DIC or those treated with placebo [5,42], with similar serious bleeding event rates. The benefits of DrotAA in patients with DIC has also been confirmed in the recent RESOLVE trial [17], in which there was a 7.8% ARR in 28-day mortality in patients with DIC treated with DrotAA.

**Thrombocytopenia**

Patients with a platelet count below 30,000/mm³ are at greater risk for bleeding, particularly intracranial haemorrhage, associated with use of DrotAA. Of deaths due to bleeding in the PROWESS trial, 66% occurred during the infusion. Of these, 75% occurred in patients with severe thrombocytopenia (platelet count <30,000/mm³). The FDA and the EMEA differ in that they consider severe thrombocytopenia relative and absolute contraindications to the use of DrotAA, respectively. Consequently, it is advisable that patients with a baseline platelet count below 30,000/mm³ be treated by those experienced in the use of DrotAA after careful evaluation of the risks and benefits for the individual patient. However, if during the infusion there is a decrease in platelet count to below 30,000/mm³, platelet transfusion should be used to maintain the platelet count above this level [43].

**Timing: importance of early use**

Identifying the period of time in which to treat patients with severe sepsis is important in terms of maximizing cost-effectiveness and decreasing morbidity and mortality. Early identification and treatment of patients with severe sepsis using standard supportive care significantly improves outcomes [44]. The ENHANCE trial suggested greater benefit in patients treated earlier (<24 hours) rather than later (>24 hours from first documented sepsis-induced organ dysfunction to treatment) with DrotAA [19].

The effect of timing of DrotAA treatment on the outcome of severe sepsis was also recently evaluated in patients receiving either DrotAA or placebo who were enrolled in five severe sepsis trials with similar entry criteria, using the INDEPTH database [45]. The study demonstrated that, compared with placebo, DrotAA treatment conferred a potential survival benefit, regardless of time to treatment (for instance, even when given late). However, the greatest reduction in mortality was observed in patients who were treated within 24 hours of developing the first organ failure [45], with no differences found in the source of infection according to timing of intervention [46].

The majority of the risk-adjusted survival benefit observed in patients receiving early DrotAA treatment was accounted for by a reduction in the number of deaths due to sepsis-induced multiple organ failure [45]. These data were again confirmed by a retrospective analysis conducted among 274 patients with severe sepsis who received DrotAA in five teaching hospitals [47]. Hospital survival was higher for patients with prompt initiation of DrotAA (same day 67.2%, next day 59.6%, later 48.4%), with an adjusted OR (95% CI) after controlling for age, vasopressors, mechanical ventilation, and other organ dysfunctions of 0.52 (0.45 to 0.60). Among those patients who received DrotAA within 24 hours, mortality rates were similar to those in DrotAA patients included in PROWESS. More recent data from a Canadian multicentre observational study [48] indicate a substantial mortality reduction (OR 0.51, 95% CI 0.28 to 0.92; \(P=0.024\)) in those patients who received DrotAA within 12 hours of diagnosis of severe sepsis. Multivariate analysis in this study identified time to treatment as an important independent but modifiable risk for death in this population.

It is acceptable, however, to make a distinction between conditions that require early treatment with DrotAA and others in which it is reasonable to allow some time to assess response to standard treatments. A group of diseases that have been shown to benefit from early treatment (within 3 to 6 hours) with DrotAA include purpura fulminans, toxic shock syndrome, meningitis with multiple organ failure, and severe CAP (for instance, *Streptococcus pneumoniae* infection). In various other conditions, infection source control and response to organ support may lead to clinical improvement within 6 to 12 hours. These situations include ascending cholangitis or pyelonephritis, secondary to obstruction, catheter-related sepsis, and intra-abdominal collections, or abscesses drained surgically or percutaneously [13]. If there is deterioration or lack of response to source control, DrotAA should be initiated in the absence of contraindications.

**Managing the infusion**

**Learning curve**

An important issue that deserves careful attention when considering the efficacy of DrotAA in clinical trials is the influence of the learning curve and the level of familiarity with the treatment protocol [49]. These factors strongly influence the survival benefit with DrotAA, as reflected by the observation that there was either no treatment effect or even higher mortality in patients treated with DrotAA in the presence of one or more protocol violations pertaining, for instance, to the timing of drug administration, the enrolment of patients receiving an excluded medication, and/or failure to administer study medication according to the protocol.

These violations appear to occur during the learning curve and are less common for subsequent patients, particularly in centres treating a large number of patients [49]. This suggests that experience in implementing the protocol may contribute to the greater observed treatment effect at high-enrolling sites. A similar effect might occur in routine clinical practice when physicians become more familiar with the indications for and optimal timing of drug administration, which was confirmed by data from the Polish registry [22].
and from a recent UK single-centre study [50]. For these reasons, the SSC guidelines strongly encourage the use of a standardized policy in the ICU for the administration of DrotAA [4].

Interaction with other therapies

Heparin

Results of the XPRESS study [18,51] indicate that concomitant prophylactic heparin does not cause a loss of efficacy and has an acceptable safety profile in severe sepsis patients receiving DrotAA treatment. There was a 2.7% increase in the risk for nonserious bleeding, but similar risk for any serious bleeding event. Co-administration of prophylactic heparin and DrotAA was also associated with a reduction in the incidence of ischaemic stroke. The greatest benefit was observed in patients who were treated with heparin at baseline and continued to receive heparin during infusion of DrotAA. In fact, those who were receiving heparin at baseline but were then randomized to receive placebo had a higher mortality and a greater incidence of serious adverse events, such as venous thrombotic events. These data suggest that in patients who are receiving or are about to receive DrotAA, prophylactic heparin should not be abruptly discontinued unless the potential risks associated with heparin outweigh the potential benefits. These data also support the contention that clinical practice decisions to treat with DrotAA and with prophylactic heparin can be made independently.

Continuous renal replacement therapy

Patients with end-stage renal failure requiring chronic renal replacement therapy were excluded from the PROWESS study. However, patients who subsequently developed acute renal failure and required continuous renal replacement therapy (CRRT) remained in the study as long as the heparin dose was below 15,000 U/day. Two main issues exist concerning concomitant use of DrotAA and renal replacement therapy: the safety of DrotAA in renal failure and the need for additional anticoagulation (systemic or regional) to preserve circuit survival time.

No increase in the incidence of bleeding events is seen in patients undergoing renal replacement therapy. Pharmacokinetic data demonstrate that DrotAA is not eliminated by haemofiltration or dialysis, and its serum concentration and drug half-life are similar in patients with or without renal failure. Therefore, no dose adjustment is required [52]. Based on these data, patients with end-stage renal failure and receiving chronic dialysis treatment should not be excluded from receiving DrotAA.

It is clear that the advantage of anticoagulation on the circuit survival time and the reduction in thrombocytopenia secondary to platelet consumption by the clotted filter must be balanced against the increased risk for bleeding, particularly in the presence of clotting abnormalities induced by sepsis. There are several possible options on how to run CRRT during the infusion of DrotAA, using one of the following: low-dose heparin, regional anticoagulation with citrate or heparin/protamine, or no additional anticoagulation. The safest option may be that of not using any additional anticoagulation during the infusion of DrotAA. DrotAA appears to be as effective as heparin in terms of circuit survival time, and often the presence of thrombocytopenia or sepsis-induced coagulopathy contraindicates the concomitant use of systemic heparin [53]. Several small studies have also confirmed that in patients at high risk for bleeding and with some degree of coagulopathy, CRRT in the absence of anticoagulation does not result in a shorter circuit survival time [54,55]. Anticoagulation can be recommenced, as per standard practice, when the infusion of DrotAA has been completed [52].

If filter survival time without additional anticoagulation is too short (<24 hours, in the absence of coagulopathy), then regional anticoagulation with citrate or heparin/protamine can be considered. Prefilter citrate anticoagulation appears to be superior to heparin [56] and has the advantage of avoiding systemic anticoagulation and the risk for heparin-induced thrombocytopenia. However, it requires a strictly protocolized practice, special dialysate/replacement fluids, and careful monitoring of acid-base balance, electrolytes and ionized calcium. In all cases, it is recommended that treatment with prophylactic heparin be continued, if the patient was already receiving it before CRRT [18,51,57].

Aspirin and warfarin

An increasing number of patients receive antplatelet drugs or warfarin for treatment or prevention of cardiovascular events. The PROWESS study excluded patients on warfarin (if used within 7 days before study entry and if the prothrombin time exceeded the upper limit of the normal range for the institution) and those receiving acetylsalicylic acid at a dose of more than 650 mg/day within 3 days before the study. However, these drugs should not represent absolute contraindications to the use of DrotAA but are warnings, and coagulation abnormalities can be corrected before starting DrotAA.

Monitoring clotting during drotrecogin alfa (activated) infusion

Both prothrombin time and activated partial thromboplastin time can be prolonged in sepsis, whereas DrotAA has a minimal effect on prothrombin time but can prolong the activated partial thromboplastin time. Therefore, a prolonged activated partial thromboplastin time cannot differentiate a coagulopathy caused by DrotAA from that due to sepsis. If coagulopathy worsens during the infusion of DrotAA, exposing the patient to a substantial risk for bleeding, then the benefits of continuing the infusion must be balanced against the possibility of bleeding events. This does not necessarily mandate stopping the infusion; DrotAA can be continued provided that correction of the coagulopathy is attempted with therapies such as fresh frozen plasma.
Cost effectiveness
DrotAA is cost-effective in the treatment of severe sepsis with multiple organ failure when it is added to best standard care [58,59]. An analysis of a UK group of patients with severe sepsis and multiple organ dysfunction estimated an additional mean cost per patient treated of £6,661, with a base-case cost per quality-adjusted life year (QALY) of £8,228 in patients with severe sepsis and multiple organ failure (based on 28-day survival data) [58]. Simulation results indicate DrotAA is a cost-effective use of resources in 98.7% of cases. In the UK the cost for patients with severe sepsis and multiple organ dysfunction is £6,637 pounds per QALY based on 28-day effectiveness data and £10,937 per QALY based on longer term follow-up data [58,59]. This cost compares favourably with the cost per QALY of other drugs (for instance infliximab [£23,936] and etanercept [£16,330]) or 6 months of ribavirin and interferon (£7,000).

Conservatively, in the UK for example, DrotAA could potentially save 500 lives annually for a cost of approximately £25 million (the UK cost for interferon-β in multiple sclerosis is approximately £50 million). Based on the NNT to save a life, DrotAA compares very favourably with other agents [7], and although the cost for the initial 4 days of treatment is high, DrotAA is less expensive if evaluated on the basis of cost per life saved.

Conclusion
All patients in the ICU with septic shock and multiple organ failure, in the absence of clear contraindications, should be considered early for treatment with DrotAA. Although DrotAA is the only drug proven effective for the treatment of this condition, some physicians still have equipoise as to its efficacy. Hopefully, the PROWESS Shock trial, which is due to enrol patients worldwide early in 2008, will give clear results and will better define the population who will benefit most from this exciting therapy.

Competing interests
DW has received lecture fees from Eli Lilly and Company (the manufacturer of drotrecogin alfa) and has acted as a consultant to Eli Lilly and Company over the past 5 years. LC declares that he has no competing interests.

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