EMERGING THERAPIES IN SEVERE SEPSIS

S J Finney, T W Evans

Introductory articles

High dose antithrombin III in severe sepsis. A randomized controlled trial


Context: Activation of the coagulation system and depletion of endogenous anticoagulants are frequently found in patients with severe sepsis and septic shock. Diffuse microthrombus formation may induce organ dysfunction and lead to excess mortality in septic shock. Antithrombin III may provide protection from multiorgan failure and improve survival in severely ill patients. Objective: To determine if high-dose antithrombin III (administered within 6 hours of onset) would provide a survival advantage in patients with severe sepsis and septic shock. Design and setting: Double-blind, placebo-controlled, multicenter phase 3 clinical trial in patients with severe sepsis (the KyberSept trial) was conducted from March 1997 through January 2000. Patients: A total of 2314 adult patients were randomized into two equal groups of 1157 to receive either intravenous antithrombin III (30 000 IU in total over 4 days) or a placebo (1% human albumin). Main outcome measure: All-cause mortality 28 days after initiation of study medication. Results: Overall mortality at 28 days in the antithrombin III treatment group was 38.9% v 38.7% in the placebo group (p=0.94). Secondary end points, including mortality at 56 and 90 days and survival time in the intensive care unit, did not differ between the antithrombin III and placebo groups. In the subgroup of patients who did not receive concomitant heparin during the 4 day treatment phase (n=698), the 28-day mortality was nonsignificantly lower in the antithrombin III group (37.8%) than in the placebo group (43.6%) (p=0.08). This trend became significant after 90 days (n=686; 44.9% for antithrombin III group v 52.5% for placebo group; p=0.03). In patients receiving antithrombin III and concomitant heparin, a significantly increased bleeding incidence was observed (23.8% for antithrombin III group v 13.5% for placebo group; p=0.001). Conclusions: High-dose antithrombin III therapy had no effect on 28-day all-cause mortality in adult patients with severe sepsis and septic shock when administered within 6 hours after the onset. High-dose antithrombin III was associated with an increased risk of hemorrhage when administered with heparin. There was some evidence to suggest a treatment benefit of antithrombin III in the subgroup of patients not receiving concomitant heparin. (JAMA 2001;286:1869–78)

Efficacy and safety of recombinant human activated protein C for severe sepsis

GR Bernard, JL Vincent, PH Laterre, SP LaRosa, JF Dhainaut, A Lopez-Rodriguez, JS Steingrub, GE Garber, JD Helterbrand, EW Ely, CJ Fisher on behalf of the PROWESS investigators

Background: Drotrecogin alfa (activated), or recombinant human activated protein C, has antithrombotic, anti-inflammatory, and profibrinolytic properties. In a previous study drotrecogin alfa activated produced dose-dependent reductions in the levels of markers of coagulation and inflammation in patients with severe sepsis. In this phase 3 trial we assessed whether treatment with drotrecogin alfa activated reduced the rate of death from any cause among patients with severe sepsis. Methods: We conducted a randomized, double-blind, placebo-controlled, multicenter trial. Patients with systemic inflammation and organ failure due to acute infection were enrolled and assigned to receive an intravenous infusion of either placebo or drotrecogin alfa activated (24 µg/kg body weight/hour) for a total duration of 96 hours. The prospectively defined primary end point was death from any cause and was assessed 28 days after the start of the infusion. Patients were monitored for adverse events; changes in vital signs, laboratory variables, and the results of microbiologic cultures; and the development of neutralizing antibodies against activated protein C. Results: A total of 1690 randomized patients were treated (840 in the placebo group and
850 in the drotrecogin alfa activated group). The mortality rate was 30.8% in the placebo group and 24.7% in the drotrecogin alfa activated group. On the basis of the prospectively defined primary analysis, treatment with drotrecogin alfa activated was associated with a reduction in the relative risk of death of 19.4% (95% confidence interval, 6.6% to 30.5%) and an absolute reduction in the risk of death of 6.1% (p=0.005). The incidence of serious bleeding was higher in the drotrecogin alfa activated group than in the placebo group (3.5% vs. 2.0%, p=0.06). Conclusions: Treatment with drotrecogin alfa activated significantly reduces mortality in patients with severe sepsis and may be associated with an increased risk of bleeding. (N Engl J Med 2001;344:699–709)

Early goal-directed therapy in the treatment of severe sepsis and septic shock

E Rivers, B Nguyen, S Havstad, J Ressler, A Muzzin, B Knoblich, E Peterson, M Tomlanovich

Background: Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit. Methods: We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups. Results: Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to baseline characteristics. In-hospital mortality was 30.5% in the group assigned to early goal-directed therapy, as compared with 46.5% in the group assigned to standard therapy (p=0.009). During the interval from 7 to 72 hours, the patients assigned to early goal-directed therapy had a significantly higher mean (±SD) central venous oxygen saturation (70.4±10.7% vs 65.3±11.4%), a lower lactate concentration (3.0±4.4 vs 3.9±4.4 mmol/l), a lower base deficit (2.0±6.6 vs 5.1±6.7 mmol/l), and a higher pH (7.40±0.12 vs 7.36±0.12) than the patients assigned to standard therapy (p<0.02 for all comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0±6.3 vs 15.9±6.4, p=0.001). Conclusions: Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock. (N Engl J Med 2001;345:1368–77)

Intensive insulin therapy in critically ill patients

G Van den Berghe, P Wouters, F Weekers, C Verwaest, F Bruyninckx, M Schetz, D Vlasselaers, P Ferdinand, P Lauwers, R Bouillon

Background: Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known. Methods: We performed a prospective, randomized, controlled study involving adults admitted to our surgical intensive care unit who were receiving mechanical ventilation. On admission, patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg/dl) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg/dl and maintenance of glucose at a level between 180 and 200 mg/dl). Results: At 12 months, with a total of 1548 patients enrolled, intensive insulin therapy reduced mortality during intensive care from 8.0% with conventional treatment to 4.6% (p<0.04, with adjustment for sequential analyses). The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than five days (20.2% with conventional treatment, as compared with 10.6% with intensive insulin therapy; p=0.005). The greatest reduction in mortality involved deaths due to multiple organ failure with a proven septic focus. Intensive insulin therapy also reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red cell transfusions by 50%, and critical illness polyneuropathy by 44%, and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care. Conclusions: Intensive insulin therapy to maintain blood glucose at or below 110 mg/dl reduces morbidity and mortality among critically ill patients in the surgical intensive care unit. (N Engl J Med 2001;345:1359–67)
Severe sepsis and its sequelae—septic shock and multiorgan failure (fig 1)—dominate the work load and mortality of non-coronary intensive care units1 with an estimated fiscal burden to the USA alone of $16.7 billion in 1995.2 Costs are particularly high in non-survivors.3 Sepsis is equally prevalent in the UK, and represents an increasing healthcare problem in the aging populations of all developed economies.1

Approximately 30% of patients with severe sepsis fail to survive,4 particularly if shock (that is, hypotension refractory to fluid resuscitation or pressor agents) or multiorgan failure intervene.5 Despite the efforts of basic scientists to elucidate the pathogenesis of sepsis and the enrolment of over 6000 patients in a variety of phase III trials evaluating putative therapeutic interventions,6 little progress has been made towards a sustained reduction in the mortality rate. However, in 2001 four randomised controlled trials of new therapies in sepsis were published, three of which showed reduced mortality in cohorts of patients undergoing specific interventions. Two trials, administering either activated protein C (APC) or antithrombin III,5 were based on the recognition that the coagulation system is implicated in the pathogenesis of the systemic inflammatory response that characterises sepsis. The other two examined how changing the way in which common agents such as insulin7 or fluids and inotropes8 are administered could favourably influence outcome in this patient population.

The coagulation system and sepsis
Most patients with sepsis have disturbances in their coagulation system ranging from minor changes in platelet count and clotting times to full blown disseminated intravascular coagulation with widespread microvascular thrombosis, consumption of clotting factors, and a bleeding diathesis. Vascular obstruction by fibrin clots may exacerbate organ dysfunction.9 This procoagulant tendency of sepsis is a consequence of increased thrombin-driven fibrin generation unchecked by physiological anticoagulation systems and fibrinolysis. A summary of this process is shown in fig 2. The upregulation of tissue factor on endothelial cells and monocytes, itself driven by proinflammatory cytokines such as interleukin 6,10 and monocyte ligation of endothelial cell adhesion molecules appears to be a key event in initiating thrombin production. Indeed, generation of plasma and monocyte tissue factor is increased in human sepsis11 and functional inhibition with a monoclonal antibody in a baboon model of *Escherichia coli* septicemia was shown to reduce both coagulopathy and mortality.12 13 The contact/intrinsic pathway is less important in initiation of the process but provides a major positive feedback loop for the generation of thrombin (fig 2). Physiological anticoagulants include tissue factor pathway inhibitor (TFPI), antithrombin III (AT), and activated protein C (APC). Many studies have demonstrated depletion of both TFPI and AT in human sepsis.12 14 Finally, fibrinolysis is prevented by upregulation of plasminogen activator inhibitor I (PAI-1).15 16

Thrombin not only induces fibrin clot generation by proteolysis of fibrinogen, but it is a central link to other inflammatory cascades. In vitro studies have shown its ability to cause cell proliferation, upregulate endothelial cell adhesion molecules, chemotactar neutrophils, and induce platelet activating factor release from endothelial cells.16 This has generated considerable interest in the role of thrombin and other clotting factors in the pathogenesis of sepsis. Indeed, clinical trials attempting to reduce thrombin production through physiological anticoagulants have been performed. APC and AT have been subjected to multicenter, randomised, placebo controlled trials,17 the results of which are presented below. An international phase III study is currently in progress for TFPI18 based on its ability to reduce mortality in septic baboons19 and a trend to reduced 28 day mortality and organ dysfunction in the largest phase II study performed so far. The therapeutic implications of modulating PAI-1 are yet to be explored.

**High dose antithrombin III (AT) in sepsis (KyberSept study)**

Antithrombin III, the major inhibitor of thrombin, is depleted in sepsis due to reduced hepatic synthesis, degradation by neutrophil derived elastases, and consumption.20 Lower levels are associated with increased mortality. Physiological levels of AT inhibit the coagulation cascade at multiple points (fig 2); the effects are catalysed by heparin. Supraphysiological doses bind in vitro to endothelially expressed glycosaminoglycans stimulating prostacyclin production, thus limiting platelet aggregation and neutrophil adhesion; this effect is inhibited by heparin.21 Based on phase II trials and successful preclinical studies, a

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**Figure 1** Consensus definition of the systemic inflammatory response syndrome (SIRS) is two or more of…

- **Temperature** >38°C or <36°C
- **Heart rate** >90 bpm
- **Respiratory rate** >20 bpm
- **PCO₂** <4.3 kPa
- **White cell count** >12 or <4 × 10⁹/l
- **or** >10% immature forms

**Figure 2** Schematic diagram demonstrating mechanisms of thrombin generation in sepsis and the two amplification feedback loops—one through factor Va and the other via factors Xla and Villla and the intrinsic pathway. Physiological anticoagulant systems and their sites of action are shown in grey. TFPI=tissue factor pathway inhibitor; AT-3=antithrombin III; APC=activated protein C; TM=thrombomodulin; EPCR=endothelial cell protein C receptor.
trial of supraphysiological doses of AT was undertaken by Warren et al (KyberSept study). Some 2341 patients were randomised to receive high dose AT or placebo, administered over a period of 96 hours. The co-administration of thromboprophylactic heparin was permitted. Approximately 25% of both groups deviated from the experimental protocol, primarily due to the administration of prohibited concomitant drugs or the violation of inclusion and exclusion criteria. There was no difference in 28 day mortality between the two groups, irrespective of whether analyses were by intention to treat or maintenance of protocol, or whether patients were AT deficient before treatment. There were more bleeding events in the treatment group (22.0% v 12.8%), particularly in those receiving heparin, even at prophylactic doses. In an a priori defined subgroup analysis, patients not receiving any concomitant heparin had lower 90 day mortality (44.9% v 52.5%, p=0.03). This observation may warrant further investigation.

Activated protein C (APC) in sepsis (PROWESS study)

Protein C levels fall in sepsis and are adversely associated with outcome. Furthermore, experimental depletion of protein C levels increased mortality in an animal model of sepsis. Protein C levels are measured using assays of activity which entail activation of protein C with snake venoms; these are distinct from assays of APC. Indeed, despite these low levels of protein C combined with less efficient thrombin dependent activation due to downregulation of thrombomodulin, APC levels may actually increase in experimental and clinical sepsis. APC acts as a physiological brake on the positive feedback loop amplifying coagulation through factors VIIIa and XIa (fig 2). It may be that APC is insufficiently increased in severe sepsis and further administration would be beneficial. Following favourable results in baboons and phase II trials in humans, an international multicentre, placebo controlled, randomised trial of APC was undertaken in patients with established severe sepsis (PROWESS study). A total of 1728 patients from 11 countries and 164 institutions were recruited. All had severe sepsis, defined by three rather than the usual two criteria together with markers of organ dysfunction. Patients received either a 96 hour infusion of placebo or recombinant APC (Drotrecogin alfa, Eli Lilly, 24 µg/kg/h) which was predicted to achieve a level 20 times higher than endogenous levels. Other aspects of critical care were not standardised, and retrospective analysis of antibiotic therapy was deemed to be appropriate in over 91%. Enrolment was suspended after the second interim analysis since the 28 day mortality on an intention to treat basis fell from 30.8% to 24.7% in the treatment group. This advantage occurred irrespective of whether patients had low protein C activity before treatment. Treatment was associated with significantly reduced plasma interleukin 6 and neutrophil levels, which may reflect reduced inflammation and thrombin generation. Neutrophil levels increased after cessation of the infusion, possibly indicating that the procoagulant state still persisted and that more prolonged dosing would have been appropriate. The treatment was complicated by a non-significant increase in the incidence of significant bleeding events (3.5% v 2.0% in controls) which occurred primarily during the infusion period and was uninfluenced by the co-administration of heparin.

Use of physiological anticoagulants in clinical practice

How can the disparity between the results of these two trials of anticoagulants be explained? Differences in trial design or the possible detrimental effect of co-administered heparin on the efficacy of antithrombin III may be important. Alternatively, APC may act by a mechanism other than inhibition of thrombin production. For example, APC inhibits the activity of PAI-1, thus promoting fibrinolysis. On the other hand, in vitro studies have shown that APC can inhibit neutrophil activation and reduce endotoxin-induced cytokine release from monocytes. These questions clearly warrant further investigation. The data from the PROWESS study have been met with great enthusiasm in the critical care community as this is the first time an intervention has been shown in a randomised, placebo controlled, clinical trial to reduce mortality in established sepsis. The study benefits from the large number of patients and their heterogeneity but suffers from questions about the exact mode of action of the drug, and whether dosing was adequate. Nevertheless, the US Food and Drug Administration considered the evidence sufficient to grant a licence for its prescription while specifying that a large number of additional studies must be carried out to explore more fully the issues identified above.

Haemodynamic goal directed therapy

Since Shoemaker’s observations in the late 1970s that survivors of major surgery had higher cardiac indices and oxygen deliveries than those who died, considerable enthusiasm for the pharmacological manipulation of these variables has been seen among intensive care specialists. Indeed, therapeutic targets for cardiac index (>4.5 l/min/m²) and indexed oxygen delivery (600 ml/min/m²) were subsequently proposed, derived from the median values of survivors in a cohort of 113 patients. Clinical trials targeting these “supranormal” goals in the perioperative period or in trauma victims showed a reduction in mortality. By contrast, studies exploring the extent to which possible benefits of attempting to achieve supranormal targets for oxygen delivery applied to other critically ill patients consistently failed to demonstrate a benefit on the mortality rate. Hayes et al studied a mixed population of 109 critically ill patients in the UK, randomising patients who did not achieve predefined physiological targets after simple fluid resuscitation into two groups, one receiving normal critical care and the other receiving a combination of dobutamine and norepinephrine with the aim of achieving a cardiac index over 4.5 l/min/m², an indexed oxygen delivery of 600 ml/min/m², and an indexed oxygen consumption over 170 ml/min/m². Contrary to their primary hypothesis, mortality was higher in the patients receiving aggressive haemodynamic management designed to achieve the predefined goals. Subsequently,Gattinoni et al presented data derived from a heterogeneous group of 762 patients in whom management aimed at achieving a cardiac index over 4.5 l/min/m² or a mixed venous oxygen saturation over 70% conferred no mortality advantage compared with patients in whom a normal cardiac index of 2.5 l/min/m² was maintained. In both studies there were difficulties in attaining goals. The increased mortality in the treatment group in the study by Hayes et al may in part be explained by the high doses of both inotrope and vasopressor used in attempts to achieve these goals, which may detrimentally affect the distribution of blood in the local microcirculation.

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While pre-emptive therapy is not possible in sepsis, Rivers et al perceived an opportunity in the emergency room at which haemodynamic interventions could be instituted much earlier in the natural history of the septic process. A total of 263 patients with severe sepsis were studied and randomised into two groups. Conventionally managed patients had therapy titrated, at the discretion of the caring physicians, to the clinical examination, mean arterial pressure of 65 mm Hg, central venous pressure of 8–12 mm Hg, and a urine output of at least 0.5 ml/kg/h. Patients were transferred to the ICU as soon as possible. The goal directed group were managed in several different manners: (1) an additional haemodynamic target of 70% central venous oxygen saturation was introduced; (2) attempts to achieve targets were performed using a defined protocol involving the sequential administration of fluids, vasopressors, red cells, inotropes and, ultimately, sedation and mechanical ventilation; (3) transfer to the ICU was delayed until patients had been managed on the protocol for at least 6 hours in the emergency room. Intensive care physicians were blinded to the patient group and subsequent care was carried out at their discretion. Patients receiving goal directed therapy had a reduced in-hospital mortality of 30.5% compared with 46.5% for those undergoing conventional management. These results are impressive, particularly since some conventionally managed patients will have effectively crossed over within the study by achieving the goals within 6 hours through conventional management, an effect that would weaken the power of the study to detect a difference.

How did the clinical management of the two groups actually differ? While both ultimately received similar amounts of intravenous fluid and inotrope, the goal directed group received these earlier, with a greater proportion of their fluids being red cell transfusions. The goal directed group subsequently required less vasopressor and less mechanical ventilation. The mortality advantage cannot be explained entirely by the avoidance of the deleterious effects of mechanical ventilation or vasopressors, and should be attributed to the timely administration of fluids and inotropes which resulted in the attainment of the combined goals for mean arterial pressure, central venous pressure, and urine output in 99.2% of patients (compared with 86.1% in the patients managed conventionally). Differences persisted during the study period from 7 to 72 hours, conventionally managed patients having higher base deficits, lactates, heart rates, and lower mean arterial pressures.

It is difficult to determine which aspect or aspects of goal directed therapy reduces mortality by driving the early administration of fluids and inotropes. Busy urban hospitals face difficulties in rapidly moving patients to their ultimate care units, which potentially holds up the administration of treatment. While delayed transfer from the emergency room potentially allows such treatments to be administered promptly, it is difficult to believe that this was a major factor in this study since conventionally managed patients still remained in the emergency room for a mean period of 6.9 hours (compared with 8.3 hours in the group receiving goal directed therapy). Alternatively, the target of 70% for central venous saturation may have revealed inadequacies in treatment to clinicians earlier. Central venous saturations are attractive therapeutic targets since they reflect the balance between oxygen delivery and consumption, especially (as in this study) if pulmonary artery catheterisation is not required. Furthermore, the therapeutic goal of 70% equates to a value that is both not “supranormal” and consistently achievable (in 94.9% of patients in this study). Indeed, in the study by Gattinoni et al a mixed venous saturation of 70% was achieved in many of the patients with a normal cardiac index; central venous oxygenation was probably higher. Increasingly, critical care physicians are aware that moderating their goals—for example, in mechanical ventilation—allows adequate homeostasis with less risk of iatrogenic injury. Finally, the goal directed patients were managed according to a strict algorithm delivered by a small and fixed group of healthcare professionals; these may accelerate decision making processes and promote early intervention. What is clear from this important study is that early administration of fluids and inotropes by a dedicated team of healthcare professionals can significantly improve mortality in a mixed group of patients with established severe sepsis. The issues of more moderated therapeutic targets and algorithm driven resuscitation need clarification.

### Intensive insulin therapy

Diabetes mellitus is associated with a poorer outcome following neurological injuries and myocardial infarction. Although this is due, at least in part, to more extensive vascular disease, hyperglycaemia is per se an independent risk factor for death following myocardial infarction and is associated with a worse neurological outcome in ischaemic brain injuries. This has prompted trials to assess the acute management of hyperglycaemia with insulin following myocardial infarction (DIGAMI study) and stroke (GIST study). These studies showed improved mortality and safety, respectively. While hyperglycaemia in non-diabetic subjects prognosticates a poor neurological outcome in traumatic head injury, possible benefits conferred through active insulin management remain unproven. Van den Berghe et al proposed that strict glycaemic control with insulin would be beneficial for critically ill patients. They hypothesised that hyperglycaemia or relative insulin deficiency would increase infectious complications, neuropathies, and organ dysfunction—effects that would be countered by the strict control of glycaemia. Over 1500 patients admitted to a single surgical intensive care unit were randomised prospectively to receive normal or strict glycaemic control. In those allocated to normal glycaemic control, insulin was commenced at a blood glucose level of 11.9 mM and targeted to achieve a level of 10.0–11.1 mM. Strict glycaemic control was provided by initiating insulin at 6.1 mM and titrating it to achieve a blood glucose level of 4.0–6.1 mM. This latter regimen was associated with significantly more hypoglycaemic episodes which, in two cases, were symptomatic. Of this strictly controlled group 98.9% required insulin at a mean daily dose of 71 IU, while in the normal glycaemic group only 39.2% received insulin with a mean daily dose of 33 IU. Total calorie intakes were identical in both groups.

The study was terminated early because ICU mortality in the group assigned to strict glycaemic control was significantly lower (4.6% v 8.0%), a benefit most apparent in patients requiring more than 5 days of intensive care and principally due to a reduction in the number of deaths attributable to multiorgan failure with a known septic focus. Benefits were conferred irrespective of the diabetic status, their APACHE II, or TISS-28 scores. Morbidity—for example, need for renal replacement therapy, incidence of bacteraemia, need for red cell transfusions, and neuropathy—was also lower in patients subjected to strict glycaemic control. Indeed, the risk of polyneuropathy, as detected by regular electromyography, directly correlated with blood glucose levels.

The value of the results was reduced by the inability to fully blind investigators to patient treatment, and the fact that the...
Emerging therapies in severe sepsis

Learning points

► Severe sepsis and its sequelae lead to significant mortality and represent a considerable clinical and fiscal burden
► The coagulation system is intimately linked to the inflammatory cascades, and may offer a therapeutic opportunity in severe sepsis. Activated protein C reduced mortality in an international multicentre, randomised, placebo controlled trial of patients with severe sepsis. Questions persist concerning its mechanism of action and optimal dosing regimens
► Prompt administration of fluids and inotropes to patients with sepsis can reduce mortality in patients with recent onset of severe sepsis. Treatment algorithms and targeting central venous oxygen saturation as a therapeutic goal may drive clinicians to administer such treatment early, but these approaches are not yet proven
► Surgical patients requiring prolonged ICU admission subjected to strict glycaemic control achieved a significant mortality benefit. It is not yet clear whether this result can be extrapolated to other patient populations with critical illness

Discussion

These are exciting times for physicians practising critical care medicine. Patients requiring treatment in an ICU have multisystem disease with significant mortality and morbidity, consuming considerable resources. However, the randomised controlled trials cited here show clear mortality benefits for those treated with activated protein C, strict glycaemic control with insulin, and the early administration of fluids and inotropes. Nevertheless, all raise questions about which groups of patients are most likely to benefit from a specific intervention, and the mechanisms whereby this is achieved. Further studies will hopefully clarify these issues and help guide our clinical practice.

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EMERGING THERAPIES IN SEVERE SEPSIS

S J Finney and T W Evans

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