New treatment strategies for severe sepsis and septic shock

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Purpose of review

Severe sepsis and septic shock are common causes of morbidity and mortality in critically ill patients. The complexities of the septic cascade continue to emerge and may identify new targets for innovative patient management. This review will highlight some of the recent advances in our management of the patient with sepsis.

Recent findings

The early administration of adequate antibiotic therapy, effective source control, and goal-directed hemodynamic resuscitation are the cornerstone of successful management. Prevention of the complications of critical illness and maintenance of normal glucose levels are also important elements of effective management. In patients with vasopressor-dependent septic shock, evaluation for inadequate cortisol response and the provision of physiologic doses of replacement steroids for those found to be deficient may result in improved survival. Administration of drotrecogin alfa (activated), (activated protein C) has been shown to improve survival in patients with severe sepsis and septic shock who have a high risk of mortality. Because of its anticoagulant properties, caution must be exercised with the use of activated protein C in those patients who meet the contraindications for its use or who have risk factors for increased bleeding complications.

Summary

Significant advances have been made in our understanding of the septic cascade and our ability to manage patients with severe sepsis and septic shock. Despite these advances, significant morbidity and mortality continue. In addition, there is also considerable impact on the financial and overall function of the patient.

Keywords

sepsis, septic shock, antibiotics, vasopressors, corticosteroids, coagulation, hyperglycemia, activated protein C

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Abbreviations

ACTH	adrenocorticotropin hormone
APACHE	acute physiology and chronic health evaluation
APC	activated protein C

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Introduction

Severe sepsis and septic shock evolve from a systemic inflammatory and coagulation response initiated as part of the body's response to a documented infection [1,2••]. The infection may be bacterial, viral, fungal, or parasitic. Past efforts to discern the true scope of this clinical problem and the true incidence have been hampered from lack of uniform agreement on the definition of sepsis and its various sequelae [1]. In 1991, the American College of Chest Physicians and Society of Critical Care Medicine convened a Consensus Conference with a goal of providing a uniform definition for sepsis and its sequelae using common clinical findings such as alteration in body temperature, tachycardia, tachypnea, or hyperventilation, and abnormalities in the white blood cell count (high, low, or increased immature cells) that were identifiable at the bedside or early in the clinical process [1]. The consensus conference provided definitions for sepsis, severe sepsis, septic induced hypotension, septic shock, and multiple organ dysfunction syndrome [1]. Despite our increased understanding, improved support, and more powerful antibiotic therapy, severe sepsis and septic shock continue to be the second leading cause of death in noncoronary intensive care units [3].

Incidence and epidemiology

Two recent studies have attempted to quantify the number of severe sepsis episodes that occur each year in the United States using ICD-9 discharge coding data [4,5]. Angus *et al.* used ICD-9 discharge diagnoses relating to infection combined with those related to organ dysfunction for seven states and extrapolated their findings for the 50 United States [4]. Their data estimate that more than 750,000 cases of severe sepsis occur each year in the United States, with a mortality rate of approximately 28.6%. They reported that the economic impact of a severe sepsis diagnosis was approximately $22,000 per case or a total of about $17 billion per year in the United States. Furthermore, these authors projected an increase in the yearly incidence of about 1.5%/y based on current trends [4]. Martin *et al.* used selected ICD-9 discharge coding data from the National Hospital Discharge Survey database and reported on the changing incidence

and scope of sepsis from 1979 to 2001 [5]. Their data suggest an annual incidence of 660,000 episodes of sepsis and its sequelae each year in the United States [5]. During the 22-year survey, the authors evaluated 10,319,418 cases of sepsis. This amounted to 1.3% of all hospital admissions. The incidence of sepsis was found to increase from 82.7 cases/100,000 population to 240.4 cases/100,000 population. Men were more likely to develop sepsis than women, and sepsis was more common in the nonwhite population. Over this 22-year observation period, gram-positive organisms became the most common identified cause of sepsis. The mortality rate over this 22-year period declined from 27.8% to 17.9% [5]. However, despite the decline in mortality rates, since there was a threefold increase in the incidence of sepsis, there was an increase in the yearly number of sepsis-related deaths [5].

Pathophysiology

The septic response is an extremely complex cascade of events that encompasses proinflammatory, antiinflammatory, humoral, cellular, and circulatory involvement [2••]. The pathophysiologic process has been recently reviewed, and attention has been brought to the contribution of apoptosis or programed cell death, which may have an important role in the organ dysfunction that often results from an exuberant septic response. [2•,6,7,8•,9] There has also been a greater appreciation of the interaction between inflammation and coagulation [10]. These effects are further highlighted by the disruption of the normal fibrinolytic response in the patient with sepsis and the intense interaction with the endothelium and endothelial cell [10].

As advances in genetic typing emerge, observations of select genetic polymorphisms have been reported to modify the susceptibility to develop sepsis and to influence the particular expression of the septic response [11–16••]. The CD-14 promoter gene polymorphism (TT-159) genotype has been observed to increase the susceptibility for and the mortality rate of septic shock [13]. A similar observation had been made with the TNF2 promoter polymorphism [14,15]. Recent observations concerning mutations involving the Toll Like Receptor-4 (TLR4) endotoxin receptor on the mononuclear cells found that the presence of the Asp299Gly/Thr399Ile allele increased the likelihood of a patient to develop septic shock from gram-negative organisms [16••]. Further advances in our ability to understand and detect the genetic composition of the host and organism may yield significant advances in our ability to diagnose and subsequently treat the patient with sepsis.

Treatment of severe sepsis and septic shock

The conventional management of the patient with severe sepsis and septic shock includes effective source control, support of hemodynamic and respiratory function, and the prevention of complications of critical illness [2••,17]. Recent reports have detailed improved survival associated with the use of physiologic doses of corticosteroids, early goal-directed resuscitation therapy, tight glycemic control, and the use of activated protein C replacement for selected populations of septic patients [18••,19–21]. There have been continued efforts to investigate new and effective means to improve patient outcome by modifying the inflammatory response, coagulation pathway, or other aspects of the septic cascade.

Early effective antibiotics and source control are the cornerstone of sepsis treatment [17,22]. Empiric broad-spectrum antimicrobial agents targeting the likely cause of the infection should be initiated as early as possible and then tailored once the culture and sensitivity results are known [22]. Restoration and maintenance of appropriate hemodynamic function is vitally important [23•]. Initial resuscitation efforts should incorporate volume infusion. Crystalloid and colloid have been shown to have equal efficacy [23•]. A larger volume of crystalloids, often liters, will typically be required, but this fluid is relatively inexpensive [23•]. A smaller volume of colloid will produce a similar improvement in volume status, but these fluids are more expensive and may alter blood coagulation. If adequate amounts of volume resuscitation do not restore appropriate hemodynamic function, then vasoactive agents, vasopressors, or inotropes will likely be necessary [23•]. The pathogenesis and management of septic shock have recently been reviewed in detail [2••,9,23•]. Recent trends have seen a movement away from the use of dopamine as the initial vasopressor agent and toward the use of norepinephrine. Unfortunately, we are currently lacking strong evidence-based data to guide the selection of the ideal vasoactive agent in the setting of septic shock. An observational cohort study reported an improved survival rate in patients managed with norepinephrine as compared with the use of high-dose dopamine with or without epinephrine [24]. Recently, there has been interest in the use of vasopressin as an adjunct to the management of the patient in shock. Vasopressin, which is stored in the posterior hypophysis, is depleted soon after the onset of shock, and a state of relative deficiency is then established [9,25,26•] Some have viewed this situation as a hormonal deficiency state and suggested that replacement infusions would be beneficial for the patient in shock (see below) [9].

There is strong evidence that early goal-directed therapy of septic shock leads to improved survival compared with more conventional management [19]. In a prospective, randomized study of 263 patients who presented to the emergency room of a major urban teaching hospital, 130 patients were randomized to goal-directed therapy, which was initiated in the emergency room. The conventional management strategy targeted a central venous pressure of 8 to 12 mm Hg, a mean arterial pressure

greater than 65 mm Hg, and a urine output greater than 0.5 mL/kg/h. The early goal-directed therapy was rapidly initiated in the emergency room, and targeted a central venous pressure of 8 to 12 mm Hg, a mean arterial pressure greater than 65 mm Hg, a urine output greater than 0.5 mL/kg/h, a central venous oxygen saturation greater than 70%, and a hematocrit greater than 30%. The early goal-directed groups received more fluid early and particularly a greater number of packed erythrocyte transfusions. Patients were assessed 6 hours and then 72 hours after admission. The group of patients assigned to early goal-directed therapy had a significantly lower Acute Physiology and Chronic Health Evaluation (APACHE) II and multiple organ dysfunction syndrome scores ($P < 0.001$) compared with conventional therapy. There was a significantly improved 28-day survival in the early goal-directed therapy patients compared with the conventional resuscitation strategy (30.5% *vs* 46.5%, $P = 0.009$), which stayed consistent through 60 days of follow-up [19]. The reason for the outcome difference between the two was twice as many deaths from sudden cardiovascular collapse among the conventional treatment group compared with the early goal-directed strategy [19].

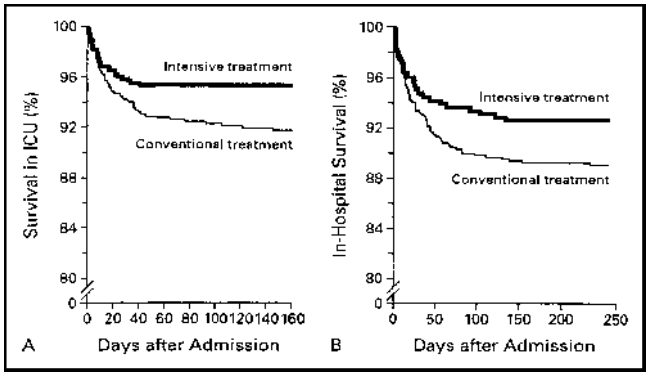
Support of oxygenation and, if necessary, ventilation is an important aspect of maintaining adequate tissue oxygen delivery [23•]. In patients who require mechanical ventilatory support, there is concern over the potential for large tidal volumes, shear forces, and alveolar overdistension to produce ventilator-induced lung injury [27,28••]. The 10-center National Institute of Health's ARDSnetwork reported the results of a multicenter prospective randomized clinical trial that demonstrated a significant reduction in mortality associated with the use of smaller tidal volumes in the management of patients with acute respiratory distress syndrome [29] Sepsis is one of the most common conditions associated with the development of acute respiratory distress syndrome, and mechanical ventilatory support is a relatively common support modality used in the management of the patient with severe sepsis and septic shock [3]. A recent report has called these results into question, proposing the end-inspiratory plateau value as the more important variable in comparison to tidal volume [30•].

Endocrine dysfunction has been a focus of recent clinical investigation in the setting of severe sepsis and septic shock, and significant advancements have been made in the area of vasopressin replacement, decreased cortisol response, and tight glucose control [9,18••,20,31]. In the treatment of vasodilatory shock, there is evidence that patients in septic shock are depleted and subsequently deficient of vasopressin, which is stored and released from the posterior pituitary gland [9,25,26•]. Vasopressin acts on V_1 receptor in the smooth muscle and V_2 receptor present in the renal collecting duct [25]. At the physiologic dose of vasopressin, 0.04 U/min, the amount of vasopressor required to maintain a mean arterial pressure greater than 65 mm Hg in patients with septic shock is reduced [25]. One randomized trial evaluated 24 patients to either norepinephrine with or without addition of vasopressin [32]. This particular trial reported a significant decrease in the amount of norepinephrine required in the vasopressin group compared with norepinephrine alone (25 μg/min to 5 μg/min versus 20 μg/min to 17 μg/min, $P < 0.05$) [32].

Another endocrine advance has been the utilization of insulin therapy as necessary to achieve tight glucose control. A prospective, randomized, controlled clinical trial evaluated 1548 patients admitted to a surgical intensive care unit to either strict glucose control of (80 to 110 mg/dL) or conventional control (180 to 200 mg/dL) [20]. Continuous-infusion insulin was often required to achieve the tight glucose control. Mortality was significantly reduced in patients managed with strict glucose control as compared with the more liberal conventional management strategy (4.6% *vs* 8.0%, $P < 0.04$) [9] (Fig. 1). There were four times as many deaths from multiple organ dysfunction with a proven septic focus in the conventional management group compared with the patients managed with intensive insulin to tightly control the blood glucose. To evaluate whether the insulin or the tight glucose control was responsible for the improved outcome, the same group of investigators used multivariate logistic regression analysis and demonstrated that the lower glucose level, not the use of insulin, was responsible for the observed decrease in mortality ($P < 0.0001$) [33•]. In addition, critical illness polyneuropathy ($P < 0.0001$), bacteremia ($P = 0.02$), and inflammation ($P = 0.03$) were also consistently improved by tight glycemic control (80 to 110 mg/dL) as compared with the dose of insulin given [33•].

For vasopressor-dependent patients with septic shock, there has been a great deal of interest and confusion

Figure 1. In-hospital and intensive care unit survival of surgical critical care patients with hyperglycemia



In-hospital and intensive care unit (ICU) survival for intensive versus conventional control of hyperglycemia in surgical critical care patients. Published with permission [20].

regarding the assessment of adrenal function and the indications for adrenal replacement therapy [34••,35•]. There have been several approaches concerning the assessment of adrenal function in the critically ill, apparently raising more questions than answers. Some advocate using a random cortisol level of more than 25 μg/dL as a threshold for adequate adrenal function in critically ill patients [34••]. In addition, they suggest the administration of replacement-dose steroids when the random stress cortisol level is less than 18 μg/dL [34••]. For those patients with an intermediate stress cortisol level between 18 and 25 μg/dL, they recommend using the 1-μg adrenocorticotropin hormone (ACTH) stimulation test rather than the traditional 250 μg, since the latter is more than 100-fold higher than physiologic ACTH levels [34••]. For those patients who are found to have lower levels of circulating cortisol during shock or in response to ACTH administration, the use of 100 mg of hydrocortisone IV every 8 hours should be sufficient replacement therapy. The important point these authors stress is that to truly stress the hypothalamic–pituitary–adrenal axis, the body should be in hypoglycemic shock [34••]. Some experts believe that any cause of shock should be an adequate stress to allow evaluation of the hypothalamic–pituitary–adrenal axis. Another proposal uses a random cortisol level of more than 34 μg/dL as an indicator of adequate adrenal function in the critically ill patient [35•]. Although controversy continues on the optimum method to evaluate hypothalamic–pituitary–adrenal and adrenal function in the patient with severe sepsis and septic shock, most would agree that if adrenal insufficiency is suspected, the patient's baseline cortisol and possibly poststimulation cortisol should be evaluated and replacement therapy should be instituted until the results of testing are available. Failure to treat adrenal insufficiency in the setting of shock can result in increased morbidity and mortality [35•].

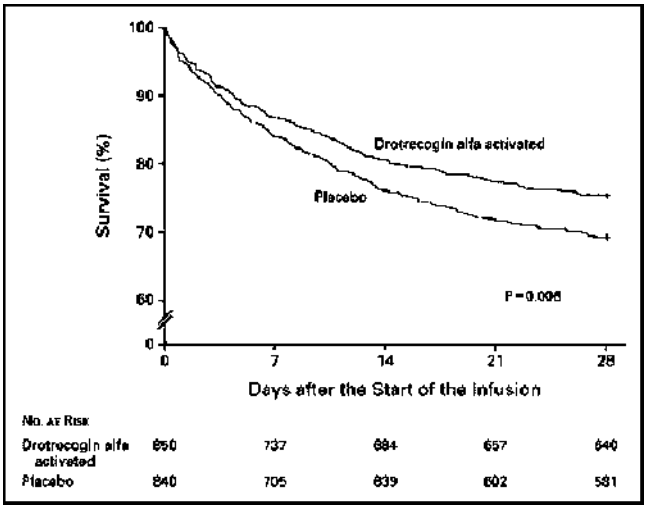
The use of corticosteroids for the treatment of patients with severe sepsis and septic shock remains controversial, despite the results of multiple clinical trials and meta-analyses. The use of steroids, in particular high-dose steroid therapy, has recently been reviewed [36,37]. Annane *et al.* reported on the baseline and post 250-μg ACTH stimulation cortisol levels in a group of patients with septic shock. The inability to increase the cortisol by greater than 9 μg/dL from baseline was associated with increased mortality [18••]. Subsequently, a multicenter, prospective, randomized, placebo-controlled, double-blind trial was conducted to evaluate more physiologic doses of corticosteroids (hydrocortisone 50 mg IV every 6 hours for 7 days) plus fludrocortisone (50 μg orally per day for 7 days) in the management of patients with severe sepsis and septic shock. Approximately 300 patients were enrolled in this trial. They were all on ventilatory support, had invasive hemodynamic monitors in place, and were resuscitated according to a protocol. All patients underwent an evaluation of adrenal function at enrollment. This evaluation included baseline and post 250-μg ACTH stimulation cortisol levels. Approximately 75% of the patients enrolled in this trial were found to have a relative adrenal insufficiency that was defined as an inability to increase the baseline cortisol more than 9 μg/dL after ACTH stimulation. In this group of patients (relative adrenal insufficiency) there was a significant improvement in 28-day survival rate. There was no increase in survival in the adrenally sufficient group or in the overall study population [18••].

The prevention of complications of critical illness is an important component of sepsis management. The patient with sepsis is subject to the various complications that are frequently encountered in the critically ill patient. Many of these complications are preventable with the use of prophylactic strategies. Among the common complications are stress-related gastrointestinal hemorrhage, deep venous thrombosis and pulmonary embolism, nutritional deficiencies, nosocomial infections, anemia, thrombocytopenia, and critical illness polyneuropathy and polymyopathy [38,39•,40]. The anemia of critical illness is an increasingly common finding in the intensive care unit [40]. This anemia is multifactorial in origin. Among the potential causes are the blood loss from phlebotomy, blood loss from procedures, iron and nutritional deficiencies, decreased erythrocyte survival, decreased erythropoietin production, and decreased bone marrow responsiveness to erythropoietin [40]. Anemia is often treated with packed erythrocyte transfusions. The use of packed erythrocyte transfusions is associated with the transmission of potential viral and bacterial infections, immune modulation, graft-versus-host disease, volume overload, and transfusion-related acute lung injury [41•,42]. Retrospective evidence suggests a significant increase in nosocomial infections with transfusion of blood products, $P < 0.005$, and that the infection risk overall is increased by factor of 1.5 [41•]. The risk of transfusion-related acute lung injury is roughly 1 in 5000 transfusions, however this figure is likely underreported. Transfusion-related acute lung injury symptoms include fever, chills, hypotension, pulmonary edema, and dyspnea [42]. Administration of packed erythrocytes has also been suspected of triggering a proinflammatory response that may serve as a "second hit" that might trigger the development of multiple organ dysfunction syndrome [43]. One alternative that can reduce the amount of blood products transfused has been through the administration of exogenous erythropoietin. Patients that are anticipated to be admitted to the intensive care unit for more than 1 week were shown to have a reduced need for allogeneic blood transfusion and had a higher 30 day hematocrit compared with the non erythropoietin treated patients [44].

In the battle against sepsis, there have been numerous failed attempts using alternative therapies [45,46•]. One

particular agent that has demonstrated mortality benefit and recently received United States Food and Drug Administration approval is recombinant activated protein C (APC) or drotrecogin alfa (detinated). APC is an endogenous anticoagulant that inhibits factor V and factor VIII [21]. In addition, APC has been shown to have antiinflammatory properties as demonstrated by decreased E-selectin and cytokine (interleukin 6) release from neutrophils [21]. Profibrinolytic effects are also demonstrated by inactivation of plasminogen activator inhibitor-1. In order for protein C to become activated, it must combine with thrombin and endothelial cell-thrombomodulin along with the endothelial protein C receptor [21]. In the setting of severe sepsis, this activation process is disrupted related to abnormalities of the endothelium, which must be intact for adequate function. There is supportive evidence that the first "organ system" adversely impacted by sepsis is the endothelium; therefore, APC supplementation is a rational therapeutic option [47]. In the prospective, randomized, multicenter, placebo controlled, double-blind PROWESS trial, 1690 patients with severe sepsis or septic shock were randomized to either a 96-hour continuous infusion of APC or placebo. The trial was stopped after a second interim analysis based on a predefined stopping rule for efficacy [21]. The study demonstrated a significant decrease in absolute all-cause risk of death of 6.1% ($P = 0.005$) and a relative reduction in the risk of death of 19% (Fig. 2). The number needed to treat to save an additional life was 16 [21]. Because APC is an anticoagulant, it is not surprising that there was a trend toward an increased incidence of severe bleeding complications in the APC treatment group (3.5% versus 2.0%); however, this did not reach statistical significance.

Figure 2. Kaplan-Meier survival curve for placebo versus activated protein C in patients with sepsis and septic shock



Kaplan-Meier survival curve over 28-day study for placebo versus activated protein C in patients with severe sepsis and septic shock. Published with permission [21].

The US Food and Drug Administration and the European Commission have recently approved the use of drotrecogin alfa (activated) for the treatment of adult patients with severe sepsis who have a high risk of mortality. The Food and Drug Administration suggests the use of severity-of-illness scoring systems (that is, APACHE II > 25), and the European Commission suggests the presence of multiple organ dysfunction as means of selecting a population with a high risk of mortality. The contraindications for the use of APC include those patients with known hypersensitivity to drotrecogin alfa (activated) and any patient with a high risk of death from bleeding or significant morbidity associated with bleeding. This would include patients with active internal bleeding, recent hemorrhagic stroke, intracranial or intraspinal surgery, severe head trauma, trauma with increased risk of life-threatening bleeding, the presence of an epidural catheter, intracranial neoplasm, mass lesion, or evidence of cerebral herniation. As with most new therapies, APC is expensive. Most institutions have developed guidelines for the use of APC based on cost and potential bleeding concerns.

The use of drotrecogin alfa (activated) has been the subject of several recent reviews and discussions [48,49,50–52•,53,54]. Most have targeted identifying the population that appears to derive the greatest benefit from its use and evaluating the long-term effects of treatment. Using the sequential organ failure assessment score, the use of APC was found to have a significantly faster resolution of cardiovascular and respiratory dysfunction compared with placebo [52•]. Using univariate and multivariate analysis to determine a predicted risk of mortality, the use of APC was found to improve survival compared with placebo when the predicted risk of mortality exceeded 30% [50•]. As expected, there have been discussions concerning the cost-effectiveness of this new agent in the treatment of patients with severe sepsis (see next section).

Economic impact of sepsis

Economics have an important impact on the administrative management of an intensive care unit and our health care system. As mentioned, the economic impact of a severe sepsis diagnosis was approximately $22,000 per case or a total of about $17 billion per year in the United States [4]. A recent analysis evaluated the cost-effectiveness of drotrecogin alfa where hospital costs were $30,032 versus $25,259 ($P = 0.067$) for APC and placebo, respectively [51•]. Investigators determined that APC was no more expensive than conventional treatment provided during a patient's intensive care unit admission. Furthermore, in the patient with severe sepsis with an APACHE II score greater than or equal to 25, the authors reported that drotrecogin alfa (activated) cost $27,400 per quality-adjusted life-year and was a cost-

effective therapy [51•]. A Canadian economic analysis of the use of APC in the treatment of patients with severe sepsis and septic shock found that it was a cost-effective therapy when used for patients with severe sepsis, APACHE II scores greater than or equal to 25, and a reasonable life expectancy if they survive the episode of severe sepsis [55•]. Medicare has also approved the use of drotrecogin alfa (activated) as a new technology and will allow additional reimbursement when this form of therapy is used in the care of the elderly medicare patient [56].

Outcome of Severe Sepsis and Septic Shock

Despite the advances in our understanding of the pathophysiologic alterations and improvements in management of patients with severe sepsis and septic shock, the mortality rate continues to be unacceptably high. Sepsis is now the 10th leading cause of death in the United States [3,4]. Mortality estimates for severe sepsis range from 28 to 50% and as high as 85% when accompanied by shock and multiple organ dysfunction syndrome [3,4]. Survivors of severe sepsis and septic shock were observed to have a higher 6- and 12-month mortality rate and a significantly lower health-related quality of life as judged by the SF-36 questionnaire [57–60].

Conclusion

Great strides have been made in our understanding and management of the patient with severe sepsis and septic shock over the past decade. Recent reports have detailed the vast numbers of patients who experience severe sepsis and septic shock in the United States and described the changing microbiology. Clinicians have also been alerted to the importance of effective source control consisting of early administration of effective antibiotics coupled with drainage procedures when indicated [61]. The use of early-goal-directed hemodynamic resuscitation and tight control of the blood glucose were found to improve the outcome of patients with severe sepsis and septic shock [19,20]. Vasopressor-dependent patients with septic shock who had inadequate cortisol release after ACTH stimulation were reported to benefit from the administration of physiologic replacement doses of corticosteroids [18••]. The use of APC in patients with high risk of mortality from severe sepsis and septic shock has been shown to be safe, cost-effective, and result in improved survival [21]. Although definite progress has been made, there is still much room for improvement. There are far too many episodes of severe sepsis each year and too many deaths from this disorder. The prognosis for survivors is still not great, with an increase in 6- and 12-month mortality rates coupled with reduced health-related quality of life compared with other critically ill patients.

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