



New approaches to the treatment of sepsis

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Because of an interplay of microbial and host factors, some patients who suffer an acute infectious insult progress to dysfunction of organ systems distant from the infectious site. Sepsis and septic shock affect an estimated 751,000 patients (3.0 cases per 1000 population) per year in the United States [1,2]. Approximately one-third of the patients who are admitted to the intensive care unit (ICU) who have sepsis develop hypotension that is unresponsive to intravenous (IV) fluids. Sepsis-associated mortality rates approximate 30% and are higher when shock is present [3–7]. Sepsis and septic shock are responsible for as many deaths each year as acute myocardial infarction (215,000 or 9.3% of all deaths) (see references [1,2,8,9]) and are the most common causes of death in the noncoronary ICU [10,11]. Using 1995 data, the average direct cost for each case of sepsis was \$22,100; the total annual costs were \$16.7 billion nationally. Moreover, the number of septic patients is projected to increase by 1.5% per year with an additional 1 million cases per year anticipated in the United States by 2020 [1].

Until recently, no specific therapies were shown to improve outcomes in patients who had sepsis [8,12]. Appropriate and timely antibiotics for the underlying infection were demonstrated to reduce mortality (see

references [6,13,14]), but the usefulness of maintenance of organ function and blood pressure with IV fluids, catecholamines, and hemodialysis has not been subjected to rigorous evaluation. A consensus conference that was sponsored by the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) sought to improve clinical trials in sepsis by providing a standard definition of the syndrome (Fig. 1) [15,16]. After decades of unsuccessful clinical studies, the last few years have found therapies that improve outcomes in septic patients. Treatment of specific populations of severely ill septic patients with drotrecogin alfa (activated) [17], corticosteroid supplementation [18], and early goal-directed therapy for hemodynamic optimization [19] has provided hope for reducing mortality rates.

Activated protein C (drotrecogin alfa [activated])

Pathophysiologic relevance to sepsis

Initial attempts to affect sepsis-related mortality were focused on modulating the inflammatory response to infection with agents, such as tumor necrosis factor (TNF)- α antibodies [3], soluble TNF- α receptor fusion constructs [20], the interleukin (IL)-1-receptor antagonist [6], and antiendotoxin antibodies [21–24]. Although these therapeutic approaches were unsuccessful in clinical trials that were conducted in the 1980s and 1990s, there was growing appreciation for the frequency of coagulation abnormalities in patients who had sepsis [25–27]. Overt disseminated intravascular coagulation (DIC) is the most well-known manifestation of a sepsis-induced dysregulation of the coagulation system [28,29]. More often, septic

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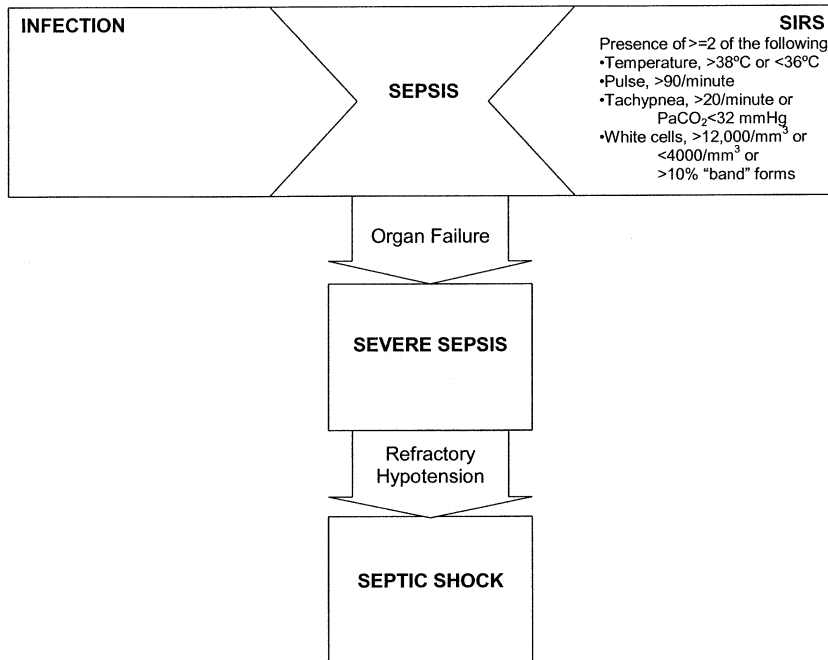


Fig. 1. The relationship between the systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock. SIRS, systemic inflammatory response syndrome.

Adapted from Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101:1644–55; with permission.

patients demonstrate less obvious abnormalities in coagulation pathways. Initially, sepsis is characterized by enhanced coagulation and endothelial activation with expression of tissue factor (TF) [30,31]. TF activates factor VII and the complex of TF and factor VIIa (TF-VIIa) activates factor X. In concert with factor Va, factor Xa converts prothrombin to thrombin, which then cleaves fibrinogen to fibrin. The fibrinolytic system is initiated rapidly by the activation of the coagulation system, but subsequently inhibition is seen in most septic patients, manifested by decreased levels of antithrombin (AT) and activated protein C and increased levels of plasminogen activator inhibitor 1 (PAI-1) (see references [25,27,28,32–34]).

Multiple inhibitory pathways exist to prevent uncontrolled intravascular coagulation. The three major inhibitors of coagulation, antithrombin, the protein C system, and the tissue factor pathway inhibitor (TFPI), seem to be affected by the septic process. Antithrombin is the main inhibitor of thrombin and factor Xa and also inhibits platelet aggregation through the release of prostacyclin (see references [27,29,35–37]). Levels of antithrombin are low in sepsis because of increased consumption, decreased synthesis, and increased deg-

radation by neutrophil elastase (see references [29,36,38,39]). Furthermore, cytokine-mediated inhibition of the expression of endothelial glycosaminoglycans reduces the effectiveness of antithrombin (see references [36,40–42]). Protein C is a second inhibitor of coagulation and is activated by thrombin that is bound to thrombomodulin on the endothelial membrane. Activated protein C (APC) inactivates factors Va and VIIIa, which limits the subsequent production of thrombin and inhibits thrombin-activatable fibrinolysis inhibitor and PAI-1, two potent inhibitors of fibrinolysis [43–48]. Between 60% and 90% of septic patients have protein C levels that are lower than normal [49,50]. Further exacerbating the decrease in protein C, increased plasma levels of C4bBP in sepsis bind protein S and reduce its free fraction, thus inhibiting an important cofactor for APC [51–53]. TFPI is the third major inhibitor of thrombin generation and inhibits the TF-VIIa complex [54–58]. Although serum TFPI levels are reduced in some *in vivo* models of sepsis, it has been difficult to show decreased levels in patients with sepsis. Depletion in sites (such as the microcirculation) may be more clinically relevant than absolute decreases in serum

levels [59–61]. In addition to effects on profibrinolytic proteins, sepsis also modulates the level and activity of inhibitors of fibrinolysis, such as PAI-1 [62]. A polymorphism in the PAI-1 gene may be related to the likelihood of developing organ dysfunction in patients who have meningococcal infection [63,64]. Sepsis-related mortality has been correlated with a variety of abnormalities in coagulation, including higher D-dimer levels, higher numbers of circulating thrombin-antithrombin complexes, higher PAI-1 levels, lower AT levels, and lower levels of protein C (see references [25,34,62,65–69]).

Coagulation activation triggers serine proteases that interact with coagulation proteins but and with cell receptors that affect inflammatory processes. Factor Xa, thrombin, and the TF-VIIa complex have each been shown to produce proinflammatory responses [70,71]. Similarly, inflammatory mediators are effective activators of sepsis-induced coagulopathy. IL-1 and TNF- α seem to act through IL-6 to increase the expression of tissue factor on endothelial cells and downregulate thrombomodulin, an activator of protein C (see references [25,27,29,72–76]). APC has anti-inflammatory properties, including decreasing proinflammatory cytokine production in endotoxin-stimulated monocytes, largely through diminishing nuclear translocation of the transcriptional regulatory factor NF- κ B, and reducing selectin-mediated adhesion of neutrophils to damaged endothelium [77–80]. APC binds to the endothelial protein C receptor (EPCR) that increases anti-inflammatory and antiapoptotic gene expression in endothelial cells [81–83]. These changes seem to be protective in severe sepsis [84]. Sepsis is associated with reduced expression of endothelial bound thrombomodulin and the EPCR, events that result in diminished generation of APC and inhibition of signaling through the EPCR [30]. The importance of the anti-inflammatory properties of APC in sepsis was demonstrated in heterozygous protein C-deficient mice. Endotoxin challenge produces more severe DIC, increased fibrin deposition, and higher levels of pro-inflammatory cytokines in these mice [85].

Clinical trials

Before the pivotal phase 3 trial of APC, preclinical and smaller clinical studies suggested that drotrecogin alfa (activated), a recombinant form of APC, might improve outcome from severe sepsis (see references [49,86,87]). Subsequently, a multicenter, international, placebo-controlled study (PROWESS) that was investigating the effect of drotrecogin alfa (acti-

vated) (Xigris) on 28-day mortality in patients who had severe sepsis was stopped because predetermined boundaries for efficacy were crossed at an interim analysis [17]. To be candidates for enrollment in PROWESS, subjects must have had: (1) known or suspected infection; (2) at least three criteria of systemic inflammatory response syndrome (SIRS); and (3) evidence of at least one dysfunctional organ system, including fluid-unresponsive hypotension, low urine output, low PaO₂/FiO₂ ratio, thrombocytopenia, or unexplained metabolic acidosis. Subjects had to be enrolled within 24 hours of the onset of the first sepsis-induced organ failure and had to begin infusion of drotrecogin alfa (activated) or placebo within 24 hours of enrollment. A total of 1690 subjects were included in the study. More than 75% of subjects required mechanical ventilation, more than 70% required vasopressors, and approximately 75% had at least two dysfunctional organ systems at enrollment. This severity of illness was reflected in an average Acute Physiology and Chronic Health Evaluation (APACHE)-II score [88] of 24.8 at enrollment and a 28-day mortality rate of 30.8% for the group that took placebo. The average time to drug administration was 17.5 hours after the onset of first organ dysfunction.

Administration of drotrecogin alfa (activated) was associated with a decrease in 28-day mortality from 30.8% to 24.7%. This significant decrease in mortality ($P = 0.005$) is equivalent to an absolute risk reduction of 6.1% and a relative risk reduction of 19.4% (95% confidence interval [CI], 6.6 to 30.5). A prospectively defined subgroup analysis demonstrated that patients who had low APACHE II scores or single organ failure had little or no benefit with drotrecogin alfa (activated) treatment [89]. Other subgroup analyses based upon gender, age, the site of infection, the type of infection (gram-positive, gram-negative, or mixed), and presence or absence of protein C deficiency showed treatment effects consistent with the beneficial results in the overall cohort [90,91]. As expected, the major clinical risk that was associated with the use of drotrecogin alfa (activated) was bleeding. Major, severe bleeding episodes (as defined as intracranial hemorrhage, any life-threatening bleeding, any bleeding classified as serious by the investigator, or any bleeding that required the administration of at least 3 units of packed red cells on 2 consecutive days [ie, a total transfusion requirement of at least 6 units of blood over 2 days]) were seen in 3.5% of patients who received drotrecogin alfa (activated) as compared with 2.0% of those in the group that received placebo ($P = 0.06$). The increased proportion of serious bleeding events was primarily related to recent trauma or instrumentation of a major blood vessel or highly

vascular organ. Subsequent evaluation of 2786 subjects who had severe sepsis in controlled and open-label trials showed a rate of intracranial hemorrhage of 0.5% (13 of 2786) during the infusion period [92]. Most bleeding occurred in patients who had platelet counts that were less than 30,000. Although severity of illness was predictive of a significant effect of drotrecogin alfa (activated) on survival, bleeding risk was not associated with greater illness severity, and occurred with approximately equal frequency in patients who had high and low APACHE II scores [90].

Subsequent to the initial study publication, the PROWESS trial and the use of drotrecogin alfa (activated) has been subject to significant scrutiny [90]. A major concern has been an amendment in the study protocol that occurred after 720 patients had been enrolled [93]. The entry criteria were modified to exclude patients who were likely to die from causes other than sepsis (eg, end-stage liver disease, transplant recipients [renal and heart transplants remained eligible]) and those in whom a commitment for aggressive treatment had not been obtained. Also, patients who had organ dysfunction for more than 24 hours at the time they met all other entry criteria were excluded. Additionally, a new placebo (0.1% albumin instead of saline) was introduced. Concerning for the interpretation of the study, is the finding by the United States Food and Drug Administration (FDA) that the efficacy of drotrecogin alfa (activated) after the amendment of the protocol differed substantially from its efficacy before the changes were made. An analysis of the effect of the protocol changes showed that the inconsistencies were limited to the patients who had lower risk of death [89]. Furthermore, among the patients who were enrolled before the change, those who would not have met the amended eligibility criteria actually had a larger absolute reduction in mortality (8%) than those whose eligibility would not have been affected by the change (1%). Also, the exclusion of a greater percentage of subjects who had chronic comorbidities may have reduced the apparent efficacy of the drug. Treatment with drotrecogin alfa (activated) was associated with a 3% absolute reduction in mortality among patients without chronic health points (assigned to patient with severe pre-existing organ failure or immunosuppression) on APACHE II, but with a 19% absolute reduction in mortality among patients who had chronic health points. In addition to the protocol amendments, a new master lot of cells was introduced during the course of the trial and used to make recombinant activated protein C. Neither the manufacturer nor the FDA was able to determine any structural or functional differences between the two lots of drug.

Ultimately, after extensive analyses that addresses the issues raised, the FDA concluded that drotrecogin alfa (activated) is safe and effective in reducing mortality among patients who have severe sepsis and a high risk of death, as determined, for example, by APACHE II score of at least 25. This final caveat was included because of the differences seen between those with higher and lower severity of illness [89]. Whether categorized by APACHE II score or by number of dysfunctional organs, patients who had more severe disease had greater benefit from treatment with drotrecogin alfa (activated). For the third and fourth quartiles of APACHE II scores (ie, APACHE II ≥ 25), the absolute risk reduction was 13%, whereas there was no absolute risk reduction for those in the combined first and second quartiles (ie, APACHE-II ≤ 24). Drotrecogin alfa (activated) also seemed to have limited benefit in patients who had single sepsis-induced organ dysfunction. Although mortality tended to increase with increasing age, the FDA analysis also suggested that drotrecogin alfa (activated) might be less effective for those who are younger than 50 years of age [90]. Because of these findings, drotrecogin alfa (activated) should be used only in the population who has severe sepsis and APACHE II scores of at least 25 or two or more sepsis-induced organ dysfunctions. Patients who are older than 50 years might receive greater benefit than younger patients. Given the anticoagulant effects of drotrecogin alfa (activated), benefits of use should be carefully weighed in patients who have a greater risk of bleeding. Subjects who have severe thrombocytopenia (platelet count $\leq 30,000$) were excluded from study entry because of excessive bleeding risk; those with extreme sepsis-induced coagulopathy (eg, international normalized ratio [INR] > 3) may also be at higher risk of treatment-associated hemorrhage. Transfusion of platelets or coagulation factors to reduce the bleeding risk that is associated with drotrecogin alfa (activated) is of unproven benefit. Therapeutic doses of other anticoagulants should be avoided and infusion of the drug should be interrupted for invasive procedures. In the PROWESS trial, infusion was interrupted 1 hour before any percutaneous procedure, such as central venous catheter or thoracostomy tube placement, or major surgery and was resumed 1 hour and 12 hours later, respectively. For those who are at continued risk of bleeding, consideration should be given for interrupting the infusion for a longer period of time. Inadvertent instrumentation while on drotrecogin alfa (activated) may be avoided by notation placed in prominent areas of the patient's chart.

A continuous infusion of 24 $\mu\text{g}/\text{kg}/\text{hour}$ drotrecogin alfa (activated) for 96 hours was used in the

PROWESS trial; the efficacy of alternative schedules is unknown. Furthermore, all infusions were begun within 48 hours of organ failure. The usefulness of later administration is unknown. An unresolved question is the efficacy and safety of drotrecogin alfa (activated) in patients who have less severe sepsis and SIRS from noninfectious causes. There is an ongoing trial for patients who have early, less severe sepsis (APACHE II score <25 or single sepsis-induced organ failure) that involves more than 11,000 subjects. Additionally, although the pivotal study did not specifically examine the interaction between drotrecogin alfa (activated) and the use of heparin for deep venous thrombosis prophylaxis, it is possible that an effect may exist [94]. Among those randomized to placebo, heparin that was used for thromboembolism prophylaxis was associated with a significantly increased ($P = 0.002$) odds of survival (odds ratio [OR] 1.66, 95% CI 1.19–2.31). A similar effect was not seen in those who were randomized to drotrecogin ($P = 0.80$, OR 0.96, 95% CI 0.67–1.38). A trial that was designed to examine such interactions is currently underway and will involve the coadministration of drotrecogin alfa (activated) with low-dose unfractionated heparin, low-dose low-molecular weight heparin, or placebo.

Because of its cost, drotrecogin alfa (activated) has been the subject of considerable economic analysis. In a 70-kg patient, a 96-hour infusion costs approximately \$7000. Two separate economic studies have been performed on the PROWESS trial data to determine the cost effectiveness of therapy [95,96]. The first study found that the cost per life-year gained by treating all patients with drotrecogin alfa (activated) was \$27,939 [95]. It was more cost effective to treat younger patients and patients who had an APACHE II score of 25. The greatest cost per life-year was seen when drug effectiveness was based upon FDA analyses of treatment of patients with APACHE II scores that were less than 25 (\$575,054 per life-year saved). The second analysis attempted to incorporate a usefulness measure (with health-related quality of life) to determine cost for quality-adjusted life-years (QALYs) [96]. Again, drotrecogin alfa (activated) was determined to be cost-effective for those with an APACHE II score of at least 25 (\$27,400 per QALY) and was cost-ineffective for those with APACHE II scores of less than 25. Drotrecogin alfa (activated) has a cost-effectiveness profile in appropriately selected patients that compares favorably with other accepted interventions, such as tissue plasminogen activator for acute myocardial infarction [97], coronary artery bypass grafting for left main vessel disease [98], and implantable defibrillators [99]. Despite these results, there was

a concern that the high acquisition cost of drotrecogin alfa (activated) may lead hospitals to restrict its use, even in patients in whom its efficacy has been determined. The Medicare, Medicaid SCHIP Benefits Improvement and Protection Act of 2000 (section 533[b], Public Law 106,554) is designed to address this issue by providing additional payments to hospitals that provide new technologies or services that substantially improve patient outcomes. The Centers for Medicare and Medicaid Services determined that drotrecogin alfa (activated) meets the required criteria, and, therefore, hospitals will receive additional compensations for appropriate use of the drug [100].

Other anticoagulants

Because of the frequency of sepsis-induced coagulopathy, other agents have been studied in severe sepsis. Numerous experimental studies in animals and phase 2, placebo-controlled trials in patients who had severe sepsis suggested that AT might provide significant protection from multi-organ failure and a survival benefit in the most severely ill septic patients [101–103]. As a result, a multicenter, international, phase 3 study of AT administration in severe sepsis (KyberSept Trial) was performed with a total of 1157 subjects [104]. All subjects had suspected infection, hyper- or hypothermia, and abnormalities in white cell count. Additionally, subjects had three of the following six criteria: (1) tachycardia (>100/minute); (2) tachypnea (>24/minute) or mechanical ventilation; (3) fluid-refractory hypotension; (4) thrombocytopenia (<100,000/mm³); (5) elevated lactate levels or metabolic acidosis; or (6) oliguria. Subjects were enrolled within 6 hours of meeting entry criteria. Overall mortality at 28 days was 38.9% in the group that was treated with AT and 38.7% in the placebo group ($P = 0.94$). Bleeding complications were significantly more common in the group that was treated with AT (22%) than in the placebo group (12.8%, $P < 0.001$).

APC and AT have similar effects on coagulopathy and inflammation. Why was drotrecogin alfa (activated) effective whereas AT was not in similar groups of patients? In comparing the seemingly disparate results of trials that had some similarity, it is helpful to examine differences in the study population, the trial protocol, and the therapeutic intervention. Both trials included severely ill septic patients, that was demonstrated by the high mortality in the placebo arms (30.8% in PROWESS and 38.7% in KyberSept). Entry criteria were comparable and both sought to select subjects who had a high risk of death from sepsis, as opposed to pre-existing comorbidities. Early intervention in the septic process was emphasized in each case.

Furthermore, each study involved the continuous infusion of the treatment for 4 consecutive days. Certainly, differences in the actions of the two agents may account for most of the observed effects on outcome. Conversely, a possible confounding factor in the AT trial was a lower than expected prevalence of reduced levels of circulating AT at study entry and a lower than expected increase in AT levels in those who received active therapy. Furthermore, AT must bind to glycosaminoglycans on endothelial surfaces or inflammatory cells to exert its anti-inflammatory effects. Heparin competitively inhibits the binding of AT to other glycosaminoglycans and eliminates the anti-inflammatory effects of AT (see references [39,105–110]). This is consistent with the findings of the KyberSept study in which those who did not receive concomitant heparin had a trend toward a beneficial effect from the administration of AT (28-day mortality, 37.8% for AT, 43.6% for placebo, $P = 0.08$).

Another anticoagulant, TFPI, showed early promise in severe sepsis [59,111], but a recent phase 3 study was terminated because of lack of efficacy [112]. Similarly, platelet-activating factor acetylhydrolase (PAF-AH) is an agent that is intended to deactivate platelet-activating factor, a mediator of inflammation and thrombosis. A phase 3 trial of recombinant PAF-AH was stopped at an interim analysis because

of a lack of benefit [113]. The results of these studies have not been published so comparisons with the PROWESS trial are not possible.

Heparin has been studied in the past for the treatment of sepsis-induced DIC [114]. Heparin has not been specifically studied in patients who have severe sepsis but who do not have DIC. Data from the PROWESS and the KyberSept studies suggest that heparin may have a role in the treatment of these patients. As proposed by Davidson et al [94] (Table 1), there is a possible benefit of heparin (either unfractionated or low-molecular weight) as a treatment for sepsis in doses that are used for prophylaxis for deep venous thrombosis. In the PROWESS trial, heparin administration alone (28-day mortality of 28.1%) had an effect similar to that of drotrecogin alfa (activated) administration alone (28-day mortality of 24.1%). The apparent benefit of heparin may reflect selection bias, however, because less severely ill patients may be more likely to receive heparin prophylaxis. Obviously, these studies were not designed to determine the specific influence of heparin on outcome and a study with this primary goal is needed to determine its efficacy. Meanwhile, other anticoagulants for targeting the coagulopathy of sepsis are currently in development or in various stages of clinical trials.

Table 1

The effect of heparin on 28-day mortality in drotrecogin alfa (activated) and antithrombin trials

Trial and treatment group	Survival at 28 Days		Odds ratio of survival associated with heparin administration (95% CI)	P value
	Yes, number of subjects (%)	No, number of subjects (%)		
Drotrecogin alfa (activated) Trial				
Placebo recipients			1.66 (1.19–2.31)	0.002
Heparin	458 (71.9%)	179 (28.1%)		
No heparin	123 (60.6%)	80 (39.4%)		
Drotrecogin alfa (activated) recipients			0.96 (0.67–1.38)	0.80
Heparin	476 (75.1%)	158 (24.9%)		
No heparin	164 (74.9%)	52 (24.1%)		
Antithrombin Trial				
Placebo recipients			1.34 (1.04–1.73)	0.03
Heparin	514 (63.5%)	296 (36.5%)		
No heparin	195 (56.5%)	150 (43.5%)		
Antithrombin recipients			0.94 (0.72–1.21)	0.62
Heparin	489 (60.6%)	318 (39.4%)		
No heparin	220 (62.1%)	134 (37.9%)		
All placebo recipients			1.45 (1.18–1.78)	<0.001
Heparin	972 (67.2%)	475 (32.8%)		
No heparin	318 (58.0%)	230 (42.0%)		

From Davidson BL, Geerts WH, Lensing AW. Low-dose heparin for severe sepsis. *New Engl J Med* 2002;347:1037; with permission.

Corticosteroid therapy

Pathophysiologic relevance to sepsis

Corticosteroids have been used as a therapy in serious infection and sepsis for decades and the data have generated considerable controversy. The first study that suggested a benefit in patients who had sepsis was published in 1951 [115] and more than 50 clinical investigations have followed. Initial enthusiasm for the use of corticosteroids was based on their well-known anti-inflammatory properties. Corticosteroids have a wide range of anti-inflammatory effects, such as preventing complement activation, reducing nitric oxide synthesis, inhibiting leukocyte adhesion and aggregation, and reducing platelet activating factor, tumor necrosis factor- α , interleukin (IL)-1, and prostaglandin production in response to a variety of stimuli [116–123]. In experimental models of sepsis, corticosteroids can reduce mortality if administered in high doses for short periods before or immediately after the initiation of an inflammatory insult [124]. Despite initial hints at efficacy [125,126], larger, randomized studies and meta-analyses failed to show a mortality benefit for short courses of high-dose corticosteroids in septic patients [127–131].

The use of corticosteroids has undergone a re-evaluation because of the realization of the frequency of relative adrenal insufficiency in critically ill patients. Early evidence for the importance of an intact and fully functioning pituitary-adrenal axis followed observations at the University Hospital of Glasgow. Between 1969 and 1980, the mortality rate among patients who had multiple injuries varied between 22% and 29% but increased to 44% in 1981 and 1982, despite the absence of changes in injury-severity scores. This increase in mortality coincided with the introduction of etomidate, a short-acting hypnotic, to the ICU [132,133]. Etomidate was a selective inhibitor of 11 β -hydroxylase, the enzyme that converts deoxycortisol to cortisol [134]. Subsequently, several studies showed that most patients who have septic shock have inadequate adrenal reserves when challenged with corticotropin (ACTH) or corticotropin releasing hormone [135–138]. Approximately 70% of mechanically ventilated patients who have fluid-refractory shock and additional organ dysfunctions have relative adrenal insufficiency (as defined as an increase in serum cortisol of more than 9 μ g/dL 1 hour after the administration of 250 μ g of ACTH) [18,139]. The presence of inadequate adrenal reserve is associated with worse outcomes, including higher mortality rates and prolonged need for vasopressor support of blood pressure, compared with those who have intact adrenal

function [135–138]. Three patterns of response to ACTH in patients who have septic shock were described and predict outcome from the acute illness [139]. The group with the lowest 28-day mortality (26%) had a baseline cortisol level of 34 μ g/dL or less and had a post-ACTH increase in serum cortisol of at least 9 μ g/dL and made up 30% of the study cohort. Highest mortality (82%) was seen in the approximately 20% of patients who had a baseline cortisol of at least 34 μ g/dL and a post-ACTH increase in cortisol of up to 9 μ g/dL. The remaining subjects had a baseline cortisol level of up to 34 μ g/dL and an increase of up to 9 μ g/dL or a baseline cortisol level that was greater than 34 μ g/dL and a post-ACTH increase in cortisol of more than 9 μ g/dL; in this group the mortality rate was intermediate (67%).

Clinical trials

The high incidence of adrenal dysfunction in septic patients that was associated with increased mortality, suggested that adrenal replacement therapy with doses and administration schedules that are closer to physiologic levels may improve survival in septic shock. Preclinical studies showed that low doses of corticosteroids improved vascular responses to catecholamines (see references [138,140,141]). For example, in healthy human subjects, vasoconstriction in response to norepinephrine is decreased for several days after endotoxin infusion, but vasoreactivity is restored to normal, pre-endotoxemia levels when exogenous corticosteroids are administered [142]. Small, single center studies supported the use of prolonged administration of low doses of hydrocortisone to decrease requirements for vasopressors and improve survival in patients who had septic shock [143–145]. These findings led to a pivotal, multi-center controlled study of corticosteroid replacement in septic shock.

A placebo-controlled, randomized, double-blind, parallel group study was performed in 19 ICUs in France to determine if corticosteroid replacement was effective in septic shock [18]. A total of 300 subjects were randomized to receive either hydrocortisone (50 mg IV, every 6 hours) and fludrocortisone (50 μ g by mouth once daily) or placebo for 7 days. The primary outcome measure was 28-day survival among the subgroup of patients who were unresponsive to ACTH, defined as a post-ACTH increase in serum cortisol of up to 9 μ g/dL. Subjects for the trial had to meet the following criteria: (1) known or suspected infection; (2) body temperature greater than 38.3°C or lower than 35.6°C; (3) heart rate faster than 90 beats/minute; (4) fluid-refractory hypotension; (5) low urine output (<0.5 mL/kg body

weight for at least one hour), or PaO₂/FiO₂ ratio of less than 280 mm Hg, or arterial lactate levels greater than 2 mmol/L; and (6) need for mechanical ventilation. Initially, elevated lactate was a separate requirement for entry but this was amended during the study. Similarly, at the beginning of the trial, subjects had to be randomized within 3 hours of the onset of shock but this was later extended to 8 hours. Of the enrolled subjects, 64.8% had an inadequate response to ACTH. Patients in this study were extremely ill, as indicated by an initial Simplified Acute Physiology Score II [146] of 58.5 and an overall 28-day mortality rate of 61% for those who received placebo. On average, subjects suffered from shock for 3.6 hours before the administration of vasopressors and received hemodynamic support for an additional 4.1 hours before study drug administration.

For the group of patients who did not respond to ACTH ($n = 229$), treatment with hydrocortisone and fludrocortisone was associated with a significant improvement in the primary outcome variable of 28-day mortality. The absolute risk reduction was 10% among those who did not respond to ACTH (63% in group that received placebo, 53% in group that received corticosteroid) and the median time to death was extended by 12 days with treatment (12 days with placebo; 24 days with corticosteroid). The adjusted OR was 0.54 (95% CI, 0.31–0.97, $P = 0.04$) in favor of corticosteroid treatment in the patients who did not respond to ACTH. For the entire study cohort, there was an absolute risk reduction of 6% (61% with placebo, 55% with corticosteroid) and an adjusted OR of 0.65 (95% CI, 0.39–1.07, $P = 0.09$). The lack of a statistically significant effect on the entire cohort was due to a nonsignificant increase in 28-mortality (53% with placebo, 61% with corticosteroid, $P = 0.96$) among subjects with an adequate response to ACTH. The 28-day survival advantage among those who did not respond to ACTH was echoed in significant improvements in ICU stay, hospital stay, and 1-year mortality and in the time to vasopressor therapy withdrawal with adrenal replacement therapy. There were no significant differences between the two groups in the rates of adverse events possibly related to corticosteroids, vasopressors, or invasive procedures.

Despite the convincing findings in this study, caution must be advised. The entry criteria were changed during the study. Although this likely had little impact on the results of the study and instead improved recruitment of subjects (by eliminating hyperlactinemia as a requirement for study entry and extending the available time for enrollment), no analysis of subjects who were enrolled before and after these

changes was provided. Also, the investigators' estimation of study size and power calculations were based upon inaccurate assumptions. For example, the 28-day mortality rate of the patients who did not respond to ACTH and who were assigned to placebo was overestimated. The treatment effect that was due to corticosteroid administration in the patients who did not respond to ACTH was lower than expected, and the prevalence of patients who did not respond to ACTH in the study cohort was higher than predicted. Furthermore, although the final analyses were performed with a two-sided formulation, the sample size calculation used a one-sided calculation. These factors likely combined to produce a sample size estimation that was at risk for being underpowered. Regardless, the positive findings of this study are convincing that, in the subgroup of patients who had septic shock and other acute sepsis-induced organ dysfunction who require mechanical ventilation and are unresponsive to ACTH stimulation, therapy with hydrocortisone and fludrocortisone improves 28-day mortality.

Although this trial provides a therapeutic option for patients who have septic shock and a high risk for mortality, several questions remain. First, debate continues over the most accurate test for determining relative adrenal insufficiency and, more importantly, those patients who are most likely to benefit from corticosteroid supplementation. In this trial, a dynamic response to ACTH administration was used. Other investigators suggested that a random cortisol of at least 25 $\mu\text{g/dL}$ is a better discriminator of relative adrenal insufficiency [147]. It also will be important to determine if corticosteroid use in those who do not have relative adrenal insufficiency is detrimental. Even in the most efficient of laboratories, it is unlikely that results of cortisol assays will be available within 8 hours. Therefore, some patients who receive corticosteroids will, in fact, have intact adrenal function. At present, it seems reasonable to administer corticosteroids (hydrocortisone and fludrocortisone) to vasopressor-dependent, mechanically ventilated patients who have septic shock and additional organ dysfunction until the results of adrenal testing are available. If adrenal function is determined to be adequate, corticosteroids can be stopped; however, the efficacy and safety of this approach has not been determined. The optimal corticosteroid formulation, dose, and dosing schedule are also not yet defined. Furthermore, the appropriateness of corticosteroid supplementation to patients who have less severe sepsis and the administration to those who have vasopressor-dependent shock for more than 8 hours is not known. Finally, recent work suggests that tight control of blood glucose levels improves

outcomes in mechanically ventilated patients in a surgical ICU [148]. Although the specific role of this therapy for those who have established sepsis is unknown, achieving the goals of that study (glucose levels of 80–110 mg/dL) will likely be more difficult in the face of corticosteroid use.

Other corticosteroid trials

Corticosteroids were one of the first therapies tried in septic patients. Despite promising results from small, uncontrolled studies, subsequent larger studies failed to demonstrate a survival advantage with short courses of high-dose corticosteroids and some suggested the possibility of harm [127–131]. There are several possible reasons why the recent study with prolonged administration of low doses of corticosteroids provided a beneficial effect, whereas previous studies were unable to show such results. The study by Annane et al [18] provided an explicit description of the study population and targeted therapy at patients who had inadequate adrenal function and were most likely to respond. The recent study included only the sickest of subjects (septic shock plus an additional dysfunctional organ and the need for mechanical ventilation), whereas earlier trials enrolled subjects who had varying illness severity. None of the earlier studies seem to approach the high baseline risk of mortality that was seen in this study. Second, the justification for corticosteroid therapy in the French trial was an attempt to supplement insufficient endogenous adrenal responses, rather than an effort to suppress inflammation. Therefore, the corticosteroid dose was modest and the duration of therapy was prolonged in comparison with earlier studies. Initial approaches used short courses of high-dose corticosteroids as anti-inflammatory agents in an attempt to attenuate the response to infection. Recent work suggests that this leads to a rebound of the systemic inflammatory response and may cause harm [149,150]. Despite the mineralocorticoid activity of hydrocortisone, fludrocortisone was also administered in the French study. This was justified by the observation that 40% to 65% of critically ill patients have high plasma renin activity and low plasma aldosterone concentrations [151,152]. Finally, despite the difficulties with sample size estimations, the current study probably benefited from improved study design. Clinical trials now require prospectively defined measures of outcome and calculations of study power. Randomization and blinding are considered essential features of current clinical studies and central study administration improves compliance with study protocols and data collection.

Hemodynamic optimization

Pathophysiologic relevance to sepsis

An area of intense early research in sepsis was an attempt to address the circulatory abnormalities that lead to tissue hypoxia. These abnormalities may include intravascular volume depletion, peripheral vasodilation, myocardial depression, and increased metabolism. Such processing may lead to an imbalance between oxygen delivery and oxygen demand that results in global tissue hypoxia or shock, which is a key development that precedes multi-organ failure and death [153]. Unfortunately, this transition from the early changes of sepsis to clinically apparent shock may occur rapidly. After shock is established, efforts that may have proved effective before its onset may no longer be beneficial. Early hemodynamic assessment on the basis of physical findings, vital signs, central venous pressure, and urinary output often fails to detect persistent global tissue hypoxia [154,155]. This has led to the use of invasive monitoring with devices, such as pulmonary artery catheters, in an effort to manipulate cardiac preload, afterload, and contractility to achieve a balance between oxygen delivery and oxygen demand. Putative end points for determining such a balance have included normalized values for mixed venous saturation, base deficit, arterial lactate concentration, tissue oxygen consumption, and mucosal pH [156,157]. Further support for such an approach comes from observations that the subgroup of critically ill patients who have supranormal values for cardiac index, oxygen delivery (DO_2), and oxygen consumption (VO_2) had improved survival compared with those who had low-normal values for the same variables [158–163].

Several studies over the last 30 years have been conducted in a variety of populations of critically ill patients in an effort to improve outcome through hemodynamic optimization and have been the subject of recent reviews [164,165]. Many of these trials suffered from design limitations, including significant crossover between study groups, a lack of blinding, and poorly defined groups of study subjects. A recent meta-analysis suggested that only seven trials met predefined criteria for inclusion for analysis [164]. Although patients who were treated in these seven studies that were designed to achieve supraphysiologic values of cardiac index, DO_2 , and VO_2 had a trend toward lower mortality rates compared with controls (relative risk 0.86, 95% CI 0.62–1.20), this result was not significant in the aggregate. Furthermore, there was significant heterogeneity in the results of the included studies. The investigators suggested that the

timing of intervention might have an effect on the observed results. The only study that suggested that maximizing DO_2 might cause harm attempted hemodynamic optimization late, using randomization after ICU admission and after fluid resuscitation had failed [166].

Early goal-directed therapy

These early efforts serve as a prelude to a recent study at a single academic tertiary care hospital that involved patients who had severe sepsis or septic shock and were identified and enrolled in the emergency department [19]. In this investigation, 263 patients were randomized to a protocol of early goal-directed hemodynamic therapy (EGDT) or to standard therapy. To be eligible for enrollment, subjects had to demonstrate two of four SIRS criteria (Fig. 1) [15,16] and had to have evidence of tissue hypoperfusion as manifested by either fluid-refractory hypotension or a blood lactate level that was at least 4 mmol/L. Response to fluid resuscitation was assessed after 30 minutes and subjects were enrolled an average of 1.4 hours after arrival in the emergency department. Although investigators were responsible for evaluating prospective subjects for inclusion in the trial and obtaining consent, execution of the study interventions was performed in a nine-bed unit in the emergency department that was staffed by an emergency physician, two residents, and three nurses who were not part of the investigative team. Those who were assigned to the EGDT arm were treated in this unit according to a prescribed protocol for at least 6 hours. The EGDT protocol sought to achieve predefined levels of hemodynamics (including central venous pressure, mean arterial pressure, and central venous oxygen saturation) through the administration of IV crystalloid and colloid, vasopressors, packed red cells, dobutamine, and mechanical ventilation, as shown in Fig. 2. The study subjects had a mean APACHE II score of 20.9 at study entry; the hospital mortality was 46.5% for the group that was given placebo; this illustrates the severity of illness in the cohort.

In-hospital mortality rates were significantly lower in the group that was given EGDT than in the standard therapy group (EGDT 30.5%, standard 46.5%, $P = 0.009$). Similarly, 28-day (EGDT 33.3%, standard 49.2%, $P = 0.01$) and 60-day mortality (EGDT 44.3%, standard 56.9%, $P = 0.03$) were significantly lower in the group that was randomized to EGDT. Although there was no significant difference in the total volume of fluid administered ($P = 0.73$) or the use of inotropic agents ($P = 0.15$) over the initial 72 hours, the timing of

therapy was different. In the group that received EGDT, patients received significantly more fluid ($P < 0.001$) and more frequently received red-cell transfusion ($P < 0.001$) and inotropic support ($P < 0.001$), including β -agonists (ie, dobutamine), during the initial 6 hours of the study period. The group that received standard therapy received significantly more fluid, transfusions, and vasopressor support during the next 66 hours than the group that received EGDT. Furthermore, during the period from 7 to 72 hours, the group that received standard therapy underwent mechanical ventilation ($P < 0.001$) and pulmonary artery catheterization ($P = 0.04$) more frequently than the group that received EGDT group. Also, of the patients who survived to hospital discharge, those who received standard therapy had a longer hospital stay (18.4 days \pm 15.0 days) than those who were assigned to EGDT (14.6 \pm 14.5 days, $P = 0.04$).

Although the results in the group that received EGDT were impressive, the rapid resuscitative efforts that were administered by the investigative staff were equally remarkable. In fact, the effects of EGDT in this study may be a product of the specific attention that was paid to those who were given EGDT while in the emergency department. The subjects who were given EGDT spent a significantly longer time in the resuscitation unit than those who were assigned to standard therapy (8.0 hours \pm 2.1 hours versus 6.3 hours \pm 3.2 hours, $P = 0.001$). For many institutions, the ability to identify septic patients, to assess the severity of disease, and to begin resuscitation that involves invasive monitoring within 2 hours of presentation is a daunting task. Similarly, the ability to dedicate specific emergency department resources for nearly continuous monitoring of these patients for up to 6 hours is challenging. Perhaps the findings of this study will inspire health care systems to make structural changes that will allow for rapid response teams to intervene in septic patients. Similar efforts have been made for those who present with acute myocardial infarctions and traumatic injuries. In an open, randomized, partially-blinded trial there is always the concern that investigator bias may affect observed outcomes. In a trial such as this one, it is nearly impossible to completely blind the investigators. In an effort to minimize this potential confounder, those who provided care in the emergency department were not involved in study design or analysis; the clinicians that assumed responsibility for patient care following the study period were completely blinded to the randomization order. Ultimately, the relevance of the findings of the EGDT investigators likely rests on the confirmation of their results in other centers and on the

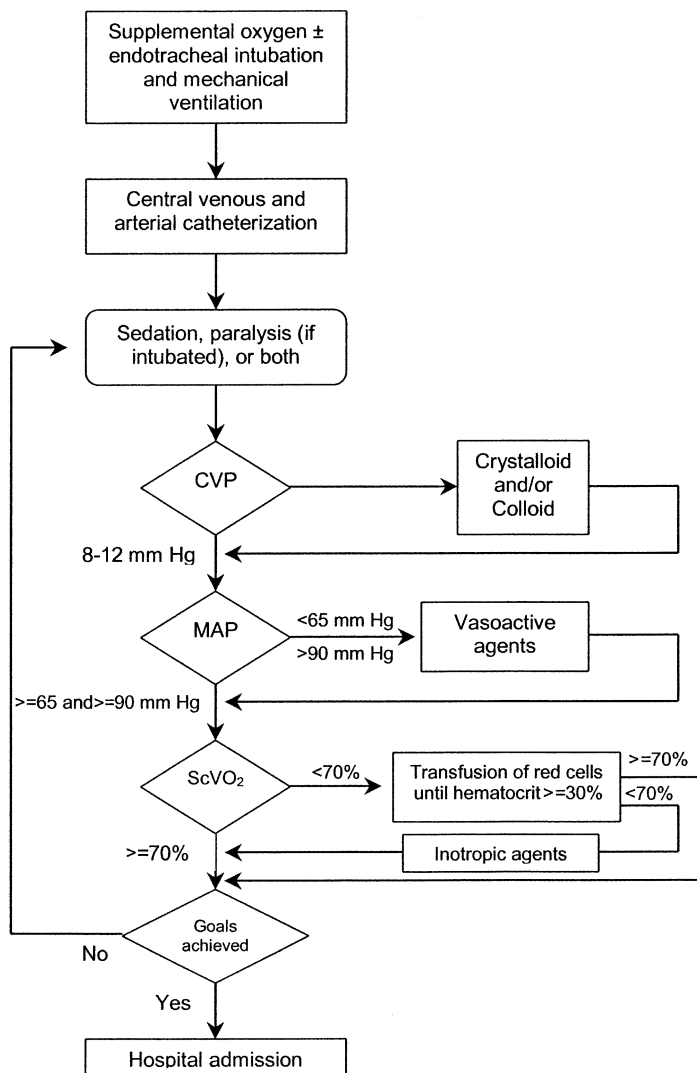


Fig. 2. Protocol used for patients who are randomized to early goal-directed therapy. CVP, central venous pressure; MAP, mean arterial pressure; ScVO₂, central venous oxygen saturation.

From Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblach B, et al, for the Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New Engl J Med* 2001;345:1371; with permission.

ability to translate their protocols to use outside of controlled trials.

As with the other trials described, the validity of the findings for septic patients who had presentations other than those included in the study is unknown. An interesting observation in the EGDT study was that of the subgroup of patients who were labeled as having “cryptic shock.” These subjects presented with a

mean arterial pressure of at least 100 mm Hg but a serum lactate level of at least 4 mmol/l; they made up approximately 25% of the study cohort. EGDT seemed to have the greatest effect in this subgroup, with a 40% absolute reduction in risk for mortality (Emanuel Rivers, MD, personal communication, 2003). This suggests that although early interventions to optimize hemodynamic parameters is effective in

those who have septic shock, greater benefit may occur in those who have signs of severe sepsis but who do not have fluid-refractory hypotension. The duration of time in which an intense resuscitative effort may still improve outcomes has yet to be defined and is also important for determining the role of EGDT protocols in the treatment of patients who have severe sepsis.

Pulmonary artery catheters and hemodynamic optimization

Despite widespread use, the clinical value of pulmonary artery catheters (PACs) in critically ill patients remains unproven [167–169]. In studies of hemodynamic optimization, PACs have often been used to measure cardiac index, DO_2 , and mixed venous oxygen saturations as indicators of resuscitation. Several studies have used a variety of therapeutic approaches in an attempt to provide hemodynamics that are believed to be associated with improved patient outcome. The protocols and study populations have varied in these trials and the results are conflicting. Recently, a multicenter, randomized, controlled clinical trial that involved blinded assessment of outcomes was completed [170]. This investigation compared therapy that was guided by a pulmonary-artery catheter (PAC) with standard therapy (not guided by a pulmonary-artery catheter) among high-risk, elderly patients who underwent surgery. Goals, in order of priority, were an oxygen-delivery index of 550 to 600 mL/minute/ m^2 of body-surface area, a cardiac index of 3.5 to 4.5 L/minute/ m^2 , a mean arterial pressure of 70 mm Hg, a pulmonary-capillary wedge pressure of 18 mm Hg, a heart rate of less than 120 beats/minute, and a hematocrit of more than 27%. Although the intervention protocol was not specified, the suggested therapy for the achievement of the goals included, in order of priority, fluid loading, inotropic therapy, vasodilator therapy, vasopressors for hypotension, and blood transfusion for a hematocrit of less than 27%. Seventy-seven of 997 (7.7%) patients who underwent surgery without the use of a pulmonary-artery catheter died in the hospital, compared with 78 of 997 (7.8%) patients in whom a pulmonary-artery catheter was used, which resulted in an absolute risk increase of 0.1% (95% CI, -2.3 – 2.5). Although there was no difference in the primary outcome, there was a higher rate of pulmonary embolism in the group that had a catheter (eight events versus zero events, $P = 0.004$). The survival rates at 6 months among patients who received standard-care and those who had a catheter were 88.1% and 87.4%, respectively (difference -0.7% ; 95% CI,

-3.6 – 2.2); negative survival differences favor standard care. At 12 months, the survival rates were 83.9% and 83.0% percent, respectively (difference, -0.9% ; 95% CI, -4.3 – 2.4). The median hospital stay was 10 days for each group.

Besides the differences in study populations (septic shock versus elderly, high-risk surgical patients), a factor that may explain differences between the EGDT and the Canadian PAC trials is the ability to reach hemodynamic goals in a timely fashion. In the EGDT study, all subjects met the mean arterial pressure goal during the initial 6 hours of study. The group that was given EGDT was more likely (94.9%) to reach the target central venous oxygen saturation ($ScVO_2 \geq 70\%$) than the group that was given standard therapy (60.2%, $P < 0.001$). The combined hemodynamic goals for central venous pressure, mean arterial pressure, and urine output were achieved in 86.1% of the group that received standard therapy compared with 99.2% of the group that received EGDT ($P < 0.001$). In the PAC study, although those who were assigned to therapy that was guided by PACs received significantly more inotropic therapy, vasodilators, antihypertensives, colloid administration, and packed red-cell transfusions, only 79.0% of the subjects achieved the goals for cardiac index and 62.9% reached targets for oxygen-delivery index. The inability to achieve the stated hemodynamic goals were also problematic in earlier studies of hemodynamic optimization and may have reduced the treatment effect [164,165]. Furthermore, the use of PACs may be an issue. A prospective cohort study that involved a mixed population of patients in medical and surgical ICUs showed that an increase in mortality, length of stay, and cost were associated with use of a PAC [171]. Moreover, even experienced clinicians and intensive care nurses often have difficulty interpreting and collecting data from PAC waveforms [172,173]. Another possible explanation is the choice of measures that are used as resuscitation end points. Attempting to manipulate cardiac output and oxygen delivery may be too difficult to achieve or these measures may not be indicative of an appropriate level of resuscitation. The EGDT study suggests that more easily obtained measures (eg, central venous saturation, mean arterial pressure) may provide more clinically relevant information, especially early in the clinical course of septic patients.

Prevention of nosocomial infection and sepsis

For those who survive the initial septic insult but remain in the ICU, nosocomial complications, particu-

larly infections, become an important issue. Avoidance of secondary infections and recurrent sepsis must be a primary goal of the health care team. A review of infection prevention in the ICU was recently published [174]. General measures include: aggressive hand hygiene [175–177], isolation of patients who have resistant organisms [178], and restriction and rotation of empiric antibiotic choices [179,180]. Ventilator-associated pneumonia, catheter-related bloodstream infections, surgical site infections, and urinary catheter-related infections make up approximately 80% of all nosocomial infections [181,182]. Interventions that were shown to reduce the incidence of ventilator-associated pneumonia include placing patients in a semirecumbent position (eg, elevating the head of the bed 45°) [183], aspiration of subglottic secretions [184], and the appropriate use of noninvasive ventilation [185,186]. Reducing the duration of mechanical ventilation with protocol-driven weaning from ventilator support [187,188] and the use of judicious sedative therapy, including daily “holidays” from sedation, seem to be beneficial [189,190]. Nosocomial sinusitis has been cited as a major risk for ventilator-associated pneumonia and can be reduced by avoiding nasal intubation with artificial appliances [191,192]. The incidence of catheter-related bloodstream infections may be reduced by the use of the subclavian insertion site and tunneled and anti-biotic-impregnated catheters [193–199]. Appropriate site preparation with chlorhexidine (rather than betadine) and maximal barriers, including large drapes, sterile gloves and gowns, masks and caps, are simple, yet effective, measures [200–202]. Removal of foreign bodies as soon as clinically appropriate can also decrease the incidence of nosocomial infections.

Intensive insulin therapy

A single-center, prospective, randomized, controlled study provides evidence that nosocomial infection may be reduced in surgical patients through tight glucose regulation [148]. A total of 1548 subjects were randomized to either conventional treatment of hyperglycemia to maintain glucose levels that were less than 200 mg/dL or to intensive insulin therapy with a goal glucose level between 80 and 110 mg/dL. All subjects were mechanically ventilated and most (63%) were enrolled in the study after cardiac surgery. APACHE-II scores were modest (median score 9) and mortality was 8.0% during intensive care among the standard therapy group. There was no significant difference in the diagnosis of diabetes or the use of insulin before study entry between the two groups.

The use of the intensive insulin protocol produced better clinical outcomes. Significantly more patients in the intensive therapy arm received IV insulin therapy (98.7%) compared with the group that received conventional therapy (39.2%, $P < 0.001$). The group that was under strict glucose control also had significantly more insulin administered per day, a longer duration of insulin use, and lower mean morning blood glucose levels. Mortality during intensive care was reduced from 8.0% to 4.6% ($P < 0.04$) with the use of tight glucose control; this benefit was attributable to the effect of intensive therapy on mortality among patients who remained in the ICU for more than 5 days (conventional 20.2%, intensive 10.6%, $P = 0.005$). Intensive insulin therapy reduced the duration of intensive care, the need for prolonged ventilatory support and renal replacement therapy, and the incidence of hyperbilirubinemia. In-hospital mortality and the incidence of critical-illness polyneuropathy were also lower in the intensive therapy arm. The greatest reduction in mortality involved deaths that were due to multiple organ failure with a septic focus, that were documented on postmortem examination. Intensive insulin treatment reduced episodes of bloodstream infections during intensive care (absolute risk reduction 3.6%, relative risk reduction 46%, $P = 0.003$) and abnormalities in markers of inflammation. Finally, although not statistically significant, among patients who had bacteremia, those who were treated with intensive insulin therapy had a trend toward a lower mortality rate than those who were treated conservatively (12.5% versus 29.5%).

Although the results that are associated with intensive insulin therapy are provocative, several limitations warrant mention. The study was conducted in a single ICU that is largely dedicated to the care of patients who have undergone thoracic surgery. The relevance of the findings to medical populations and those who are not mechanically ventilated is unknown. Similarly, the study population was at risk for sepsis but was not septic at the time of enrollment. Because it was not feasible to perform the study with strict blinding, potential bias must be considered. The investigators tried to minimize bias by assigning adjustment of insulin doses to study nurses and physicians who were not involved in clinical decision-making. An obvious concern with such tight glucose control is the occurrence of hypoglycemia. A low rate of hypoglycemia (blood glucose up to 40 mg/dL) was reported in the arm that received intensive insulin (39 patients) although it was higher than in the arm that received conventional therapy (six patients). These episodes were generally asymptomatic or associated with mild symptoms and did not lead to any identifiable hemo-

dynamic deterioration or seizures. Although there was no analysis of the number of glucose checks that was performed per patient, intensive insulin therapy did not lead to a greater number of red-cell transfusions. Finally, aggressive nutritional support was instituted in all patients as part of the study protocol. No description of the percentage of patients who received parenteral versus enteral nutritional approaches was provided nor was the total or mean calories that was provided to subjects in each group supplied. Differences in nutritional approaches could confound the findings of the study if asymmetrically distributed between the two groups. Larger studies with a broader range of critically ill patients are needed to confirm the validity of these exciting findings.

Support of dysfunctional organ systems

Cardiovascular system

Catecholamines

In patients who have septic shock, catecholamines are frequently used to increase blood pressure and improve organ perfusion. Dopamine, epinephrine, and norepinephrine are most commonly administered for septic shock and have different degrees of agonism of α - and β -adrenergic receptors. In general, α -adrenergic stimulation results in vasoconstriction, whereas β -adrenergic stimuli affect the heart and the vasculature. β_1 -stimuli have an inotropic and chronotropic effect in the heart and are capable of increasing cardiac output, whereas β_2 -receptors mediate vasodilation. Epinephrine, norepinephrine, and dopamine have mixed α - and β -adrenergic effects. In contrast, phenylephrine is a pure α_1 -agonist and causes vasoconstriction without any inotropic actions. Dobutamine (a pure β -agonist) has the expected inotropic, chronotropic, and vasodilatory effects and is used most commonly in patients who have septic shock and decreased cardiac output [10,203]. It is generally combined with catecholamines with vasoconstricting effects to counteract its vasodilatory actions. In addition to their hemodynamic effects, catecholamines modulate immunologic function, including the release of proinflammatory cytokines in endotoxin-stimulated macrophages and neutrophils and in experimental models of sepsis [204–207]. The relevance of these immunomodulatory effects on outcomes from clinical septic shock is unknown. Despite their frequent use in septic shock, there are no clinical studies that show a benefit of catecholamine vasopressors in such patients.

Several studies have compared the physiologic effects of different catecholamines in septic shock

[208–213]. Epinephrine decreased splanchnic perfusion and mucosal pH, and increased the incidence of lactic acidosis when substituted for dopamine or norepinephrine (see references [211,213,214]). Only limited data are available to show differences in the physiologic effects of norepinephrine and dopamine (see references [208,210,212]). Dopamine and norepinephrine have similar effects on renal function (see references [208,209,215–217]) and dopamine may result in greater splanchnic acidosis and greater inhibition of splanchnic oxygen use than norepinephrine [210]. Although no randomized studies have compared dopamine and norepinephrine in septic shock, observational studies suggest a higher rate of hemodynamic response with norepinephrine use [208,209]. Although not conclusive, these findings suggest that norepinephrine may be preferable as a first-line agent for fluid-refractory hypotension.

Most commonly, the doses of catecholamines are titrated to achieve arterial blood pressure that is adequate to perfuse end organs, and is often measured by parameters, such as mentation and urinary output. Such effects usually occur at a mean arterial pressure that is greater than 60 to 70 mm Hg or a systolic blood pressure that is greater than 90 mm Hg. Those patients who have pre-existing hypertension or vascular disease may require greater pressures to maintain perfusion. Usual doses of dopamine are between 5 and 20 $\mu\text{g}/\text{kg}/\text{minute}$ and those for norepinephrine range from 0.1 to 1 $\mu\text{g}/\text{kg}/\text{minute}$ to maintain adequate levels of blood pressure. Higher doses may be required but are associated with increasing toxicity, including arrhythmias, peripheral vasoconstriction, and lactic acidosis. Although combination therapy is often used, there is no evidence that such an approach is superior to the use of higher doses of a single agent. In patients who are initially treated with dopamine, but are unresponsive to higher doses (eg, $>20 \mu\text{g}/\text{kg}/\text{minute}$) or who suffer adverse effects (eg, dysrhythmias), it is reasonable to switch to therapy with norepinephrine because it seems to have a higher rate of blood pressure response [208,209].

Vasopressin

Vasopressin, or antidiuretic hormone, is synthesized in the hypothalamus and released from the posterior pituitary in response to hypotension, hypovolemia, or hyperosmolality [218,219]. Vasopressin that binds to V1-receptors on the systemic vasculature produces increases in arterial blood pressure in normal humans when plasma levels exceed 50 pg/mL. Activation of V2 receptors in the kidney regulates urinary osmolality by increasing cortical and medullary duct permeability and the resorption of free water. Vaso-

pressin also enhances the vascular sensitivity to catecholamines, promotes pulmonary arterial vasodilation, and aggregates platelets. In healthy humans, plasma vasopressin levels are less than 4 pg/mL and increase to 10 to 20 pg/mL in hypovolemic shock. Despite profound hypotension, plasma vasopressin levels are generally in the normal range during septic shock [218,220]. This is particularly common in patients who have prolonged catecholamine-dependent hypotension which possibly reflects depleted production or stores in the neurohypophysis [221].

In patients who have catecholamine-dependent septic shock, infusion of vasopressin, between 0.01 and 0.04 U/minute, often results in increased blood pressure and a decreased need for catecholamines (see references [220,222–226]). In a study of patients who had septic shock in which catecholamines were titrated to maintain arterial blood pressure at stable levels, vasopressin administration did not affect cardiac output but increased urine output and creatinine clearance [223]. Such results suggest that infusion of vasopressin at less than 0.04 U/minute may be useful in patients who have severe septic shock or renal compromise. Higher doses seem to increase the risk of coronary vasospasm and impair splanchnic blood flow, however. Furthermore, it is unknown if vasopressin use results in sustained improvement in organ function or increased survival in septic shock. Large, multicenter trials that compare vasopressin and catecholamines with catecholamines alone are underway.

Low-dose dopamine

Because of its more selective agonism of dopamine-receptors at certain doses, clinical studies compared low doses of dopamine with placebo in critically ill patients who were at risk for the development of acute renal dysfunction (see references [224, 227–234]). Although dopamine increases renal blood flow and urine output at doses of 1 to 3 $\mu\text{g}/\text{kg}/\text{minute}$ [235], the Australian and New Zealand Intensive Care Society's (ANZICS) study of critically ill patients who had SIRS found that dopamine (2 $\mu\text{g}/\text{kg}/\text{minute}$) had no effect on mortality, the requirement for renal replacement therapy, or peak serum creatinine [227]. Similarly, in a study of a monoclonal anti-TNF- α antibody in septic shock (NORASEPT II), a retrospective analysis found that "low-dose" dopamine did not reduce mortality, the incidence of acute renal dysfunction, or the need for dialysis [234]. Because doses of dopamine in this range can increase myocardial oxygen consumption, induce arrhythmias, and decrease splanchnic perfusion, there is no current indication for the use of "low-dose" dopamine to preserve renal function in septic patients. A newer agent, fenoldo-

pam, has specific action at the dopamine₁-receptor and may provide renovascular effects that reverse sepsis-induced hypoperfusion [236–241]. This drug also has antihypertensive effects and may have limited applications in septic patients, however. Clinical experience with fenoldopam in critically ill patients is limited (see references [238,242–245]).

Respiratory system

Sepsis is a major risk factor for the spectrum of inflammatory lung disease known as acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) [246,247], which is characterized by hypoxemia and bilateral pulmonary infiltrates in the absence of congestive heart failure [248–250]. The development of respiratory failure that requires mechanical ventilation in patients who have sepsis is associated with increased mortality [251]. As with clinical trials that involved septic patients, studies that aimed to reduce mortality from ALI/ARDS have yielded largely negative results [252–254]. The 10 university centers of the NIH Acute Respiratory Distress Syndrome Network (ARDS Network) completed a randomized study that compared two protocols for ventilator management that demonstrated a significant effect on mortality [247]. Patients were eligible for inclusion if they had an acute decrease in the PaO₂/FiO₂ ratio to 300 or less, bilateral pulmonary infiltrates, requirement for mechanical ventilation, and absence of clinical or measured evidence for left atrial hypertension; patients were enrolled within 36 hours of meeting entry criteria. A total of 861 subjects were enrolled and randomized to one of two ventilator protocols using either tidal volumes of 12 mL/kg of ideal body weight (IBW) or 6 mL/kg IBW. The study was terminated at an interim analysis because the 6 mL/kg IBW demonstrated a significant improvement in hospital mortality rates (31.0% for 6 mL/kg, 39.8% for 12 mL/kg, $P = 0.007$). The 6-mL/kg strategy also resulted in a higher rate of achieving nonassisted ventilation, more ventilator-free days, and a greater number of days without nonpulmonary organ failure.

Although this study was not specifically designed to evaluate ventilator management in patients who had severe sepsis, it provides guidance for those who have sepsis-induced respiratory failure. Approximately 27% of subjects had sepsis designated as the primary reason for ALI/ARDS and 34% had pneumonia as the leading risk factor. Furthermore, at study entry, subjects had an average of 1.8 dysfunctional organ systems. Therefore, many of these subjects likely suffered from ALI/ARDS as a manifestation of sepsis-induced organ dysfunction. Although it is unknown if septic

patients who had respiratory failure that was due to other causes (eg, mental status deterioration) or who had less severe hypoxemia benefit from such a ventilator strategy, sepsis-induced ALI/ARDS should be treated with a ventilatory strategy in keeping with the ARDS Network study.

Renal system

The mortality rate among patients who have acute renal failure is high; this has been cited as an independent risk factor for death in some studies of septic patients [255,256]. More than 50% of patients who require dialysis for acute renal failure die; this rate is especially high among those in ICUs (see references [253,257–259]). A single-center study assigned patients who had acute renal failure to either alternate-day intermittent hemodialysis or daily intermittent hemodialysis in an attempt to improve outcomes [260]. Patients who had a clinical diagnosis of severe acute tubular necrosis that was caused by a recent ischemic or nephrotoxic injury with an anticipated need for intermittent hemodialysis for at least 1 week were included. Patients who were deemed too hemodynamically unstable to tolerate intermittent hemodialysis received continuous renal-replacement therapy

and were excluded from consideration. Parenteral nutrition was provided during the hemodialysis sessions if oral intake was determined to be insufficient. Consecutively enrolled patients were assigned to one of the two arms in alternating order. In the 160 subjects who were included in the study, daily hemodialysis reduced mortality within 14 days of the last hemodialysis session from 46% to 28% ($P = 0.001$). More subjects in the group that received alternate-day hemodialysis developed anuria, SIRS or sepsis, respiratory failure, change in mental status, gastrointestinal bleeding, and hypotension during hemodialysis.

This study of alternate versus daily intermittent dialysis did not specifically target sepsis-induced renal dysfunction. Approximately 36% of subjects had sepsis identified as the primary risk factor for acute renal failure. Therefore, the findings may have some relevance for patients who have severe sepsis or septic shock. Unfortunately, problems in study design limit its findings. First, the subjects were not assigned to a study arm by a randomization scheme; instead they were allocated to treatment on an alternating basis. Also, those who were assigned to alternate-day hemodialysis received a lower percentage of the prescribed hemodialysis dose than those who received hemodialysis daily. Thus, undertreatment in

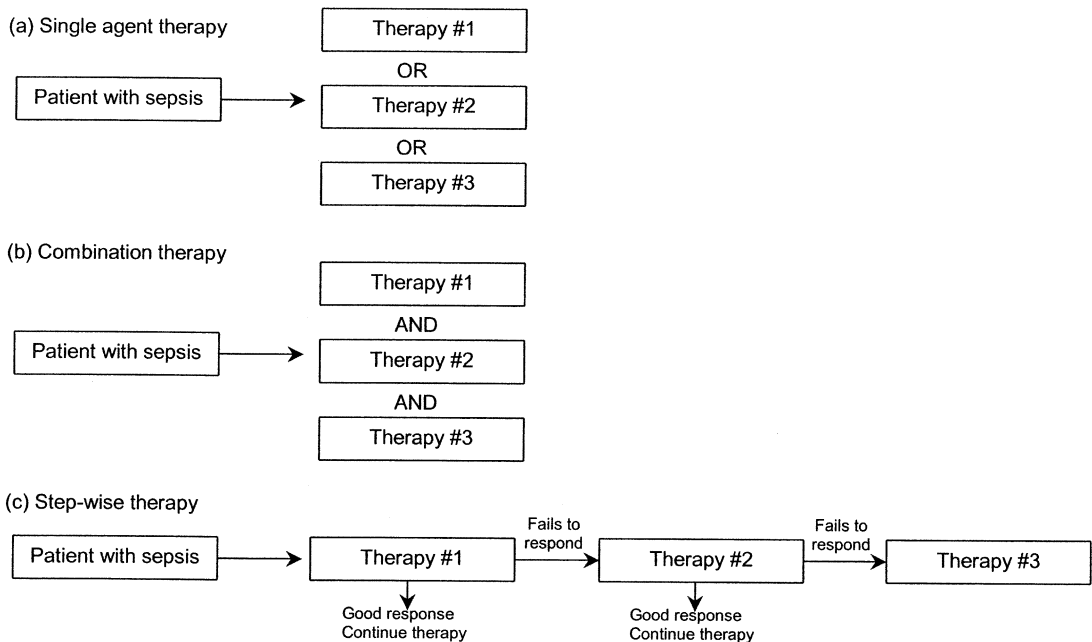


Fig. 3. Hypothetical strategies for the provision of therapeutic interventions in patients who have sepsis, severe sepsis, and septic shock.

the group who received alternate-day treatment may have been a more important factor in the outcome than the frequency of hemodialysis. A more intensive regimen in the group who received alternate-day hemodialysis may have reduced or eliminated the differences between the two groups [261]. Finally, the mortality in the group who received alternate-day hemodialysis was 46%, which is lower than the rate in most studies of acute renal failure in patients in the ICU. Furthermore, patients who needed continuous renal replacement at initial evaluation were excluded from the study cohort; therefore, it is likely that patients who had less severe illness were preselected for enrollment.

Single, combination, and step-wise therapy

There is growing optimism that it is possible to have a beneficial impact on the outcome of sepsis and septic shock. This enthusiasm should be tempered by an awareness of the populations that were included in the positive trials to date. Furthermore, data are unavailable to determine the appropriate integration of the interventions that were shown to affect mortality. Obvious options for using these therapeutics are shown in Fig. 3 and include: (1) selecting the single most “appropriate” therapy based upon previous trial results and the individual patient’s level of risk; (2) providing care that incorporates all approved modalities at the earliest possible moment; or (3) implementing an initial modality, assessing the response to this therapy, and adding additional therapies for those who fail to improve. The specific approach that is chosen will likely reflect clinician preference, the individual patient’s risk for beneficial and adverse effects, and the structure of the health care system that is providing care.

Characteristics of the individual studies provide insight applicable to patient care (Table 2). The shortest time to intervention was used in the EGDT trial (<2 hours), followed by corticosteroid therapy (8 hours) and drotrecogin alfa (activated, 48 hours). These times provide targets for the interval during which proof of efficacy exists. Use of a single agent may limit options for a patient who does not respond to the initial modality chosen. For example, if a patient is given drotrecogin alfa (activated), an immediate effect may not be seen. If the clinician chooses to monitor the progress of the patient, s/he may lose the opportunity to provide additional, proven therapies. If, instead, maximal therapy is provided at presentation, the patient may have responded to a single therapy and may be subjected to risks that are

associated with additional modalities that ultimately were unnecessary. If a step-wise approach is used, therapeutic interventions are based upon timing of presentation and severity of illness. Although clinical trials that investigate the integration of the various treatment options are needed to provide definitive evidence, such an approach is a reasonable method to maximize therapeutic effect, reduce adverse events, and appropriately use limited economic resources.

Future directions

Defining diseases

The ACCP/SCCM consensus conference definitions of sepsis, severe sepsis, and septic shock [15,16] have helped to better define subjects that are included in clinical trials. Ultimately, however, these descriptions define syndromes and do not include a reference to the underlying pathophysiology. Patients who have *Escherichia coli* urosepsis are lumped with subjects who are suffering from bacteremic *Streptococcus pneumoniae* pneumonia. These patients are likely to have different pathophysiologic processes. Unfortunately, the most expeditious and accurate definition is based upon the apparent clinical syndrome. Ultimately, specific disease must be defined on the basis of the infecting organism, the site of infection, the duration of infection, and host factors that interact to produce the clinical presentation. Such a lack of appreciation of the multiple processes that are contained within the broader category of “sepsis” may be partly responsible for the failure of many clinical trials to show effect. For example, anticytokine mediators are unlikely to be effective in patients who do not have elevated levels of these cytokines; antiendotoxin antibodies are doubtful to have a benefit in patients who have with Gram-positive infections. A variety of genetic polymorphisms has been associated with outcomes from sepsis in case-control studies (see references [64,262–266]). A prospective confirmation of these associations may lead to better identification of patients who are at risk for sepsis-associated mortality and morbidity. In this way, risk stratification in the future may involve clinical features, microbiologic factors, and genetic susceptibility. By providing more specific descriptions of the sepsis syndrome and by considering the underlying pathophysiology, therapeutics can be tested in a more homogenous population who has an increased likelihood of response; care can be individualized for each patient on the basis of the specific characteristics of his or her disease.

Table 2
Selected characteristics of recent studies in severe sepsis that were shown to improve clinical outcomes

	Study design				Study results				
	Infection criteria	SIRS criteria	Criteria for dysfunctional organs or systems	Time to inclusion specified in study protocol	Primary outcome	Actual time to inclusion (mean)	Mortality of control group	Number needed to treat	Other considerations
Early goal-directed therapy ^a		Two of four SIRS criteria: Hypo- or hyperthermia Tachycardia Tachypnea WBC abnormality	One of the following: Fluid unresponsive hypotension Lactate = 4mmol/L	Upon arrival to ED	In-hospital mortality	1.4 hours after arrival	46.5%	7	Structure for rapid assessment and resuscitation; requires central venous and arterial access.
Hydrocortisone and fludrocortisone ^b	Documented or strongly suspected site of infection	All of the following: Hypo- or hyperthermia Tachycardia	All of the following: Fluid unresponsive hypotension Mechanical ventilation AND One of the following: Low urine output Low P/F Ratio Lactate >2mmol/L	Within 8 hours of onset of hypotension	28=day survival in nonresponders	7.7 hours after onset of hypotension	61% ^d	10 ^d	Rapid discrimination of nonresponders to ACTH needed; uncertain benefit in responders to ACTH
Drotrecogin alfa (activated) ^c	Known or suspected infection	Three of four SIRS criteria: Hypo- or hyperthermia Tachycardia Tachypnea WBC abnormality	One of the following: Fluid-unresponsive hypotension Low urine output Low P/F Ratio Platelets = 80,000/mm ³ or 50% decrease Unexplained metabolic acidosis	Within 48 hours after first sepsis-induced organ dysfunction	28=day mortality	17.5 hours after first organ dysfunction	44% ^e	8 ^e	Bleeding risk; other exclusion criteria; FDA approved only for those with APACHE II score of 25 or 2 sepsis-induced organ dysfunctions.

^a Data from Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New Engl J Med* 2001;345:1368–77.

^b Data from Annane D, Sébille V, Charpentier C, Bollaert PE, Francois B, Korach JM, et al. Effects of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862–71.

^c Data from Bernard GR, Vincent J-L, Laterre P-F, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *New Engl J Med* 2001;344(10):699–709.

^d For nonresponders to ACTH.

^e For APACHE II score of 25.

Challenges to future research

Despite recent advances, clinical trials in critically ill patients remain challenging. Because sepsis and its related syndromes carry significant mortality and morbidity, the ICU is an emotionally charged environment for patients and their loved ones. Because of the effect of the acute illness on the capacity of the patient, decision-making often falls to family members and friends. When one considers the need to evaluate study candidates, identify surrogate decision-makers for the patient, and complete the informed consent process, the available time to enroll study subjects and initiate the experimental protocol is limited. Studies that involve proxy-consent receive considerable attention in an effort to protect the rights of the individual patient. The standards of informed consent for experimental studies exceed those for therapeutic intervention. Although these important measures serve to safeguard patient rights, they also make enrollment and recruitment of study subjects more difficult. Equipoise must be struck between the concepts of the patient's right to refuse to participate (autonomy), the protection against risk (beneficence), and the patient's right to enter potentially beneficial studies despite his or her inability to provide consent because of the effect of the disease itself (justice).

As more trials provide effective therapeutic options for septic patients, the ability to integrate these treatments into protocols for subsequent studies will be essential. This will provide a significant challenge because individual therapies may have an independent influence on outcomes, synergistic effects, or antagonistic actions. A priori defined subgroup analysis and multivariate analyses will be needed to define the contribution of each intervention. For example, retrospective analyses of the PROWESS database found that coincident use of corticosteroid supplementation has no detrimental influence on the effect of drotrecogin alfa (activated) in severe sepsis. Furthermore, the role of the process and structure of delivered care must be appreciated and its effect on outcome understood. For example, most clinical trials in sepsis are conducted at tertiary-care academic hospitals, whereas a minority of actual critical care in the United States is practiced in this setting. Also, differences in care between different countries must be recognized. Clinical trials have focused on traditional outcomes of mortality and length-of-stay. In the future, attention must be paid to patient-oriented outcomes, such as functional status and health-related quality of life, to ensure that interventions do not result in severely compromised survivors [267]. These evaluations also allow for a better apprecia-

tion of the economic consequences of new therapeutic initiatives.

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