

Treatment of severe sepsis: where next?

Current and future treatment approaches after the introduction of drotrecogin alfa

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Abstract: Severely septic patients continue to experience excessive morbidity and mortality despite recent advances in critical care. Although significant resources have been invested in new treatments, almost all have failed to improve outcomes. An improved understanding of sepsis pathophysiology, including the complex interactions between inflammatory, coagulation, and fibrinolytic systems, has accelerated the development of novel treatments. Recombinant human activated protein C (rhAPC), or drotrecogin alfa (activated) (DAA), is currently the only US Food and Drug Administration (FDA)-approved medicine for the treatment of severe sepsis, and only in patients with a high risk of death. This review will discuss the treatment of severe sepsis, focusing on recent discoveries and unresolved questions about DAA's optimal use. Increasing pharmacological experience has generated enthusiasm for investigating medicines already approved for other indications as treatments for severe sepsis. Replacement doses of hydrocortisone and vasopressin may reduce mortality and improve hypotension, respectively, in a subgroup of patients with catecholamine-refractory septic shock. In addition to discussing these new indications, this review will detail the provocative preliminary data from four promising treatments, including two novel modalities: antagonizing high mobility group box protein and inhibiting tissue factor (TF). Observational data from the uncontrolled administration of heparin or statins in septic patients will also be reviewed.

Keywords: septic shock; drotrecogin alfa, vasopressin, new therapies, statins, high mobility group box protein

Introduction

Severe sepsis represents one of the most common diagnoses in patients admitted to the intensive care unit (ICU). This systemic inflammatory response to an infectious stimulus resulting in organ dysfunction (Bone et al 1992; Levy, Fink, et al 2003) afflicts more than 750 000 patients (Martin et al 2003) and consumes almost 17 billion healthcare dollars in the US each year (Angus et al 2001). Although sepsis without organ dysfunction is a relatively benign condition, severe sepsis results in more than 225 000 deaths in the US annually (Angus et al 2001; Martin et al 2003). Furthermore, an aging population and growing number of immunosuppressed patients treated in an environment of emerging antibiotic resistance and expanding use of invasive procedures will almost assuredly increase the burden of sepsis even further (Martin et al 2003).

Although patients with the above predispositions experience higher incidences of sepsis, the syndrome can affect anyone, including previously young, healthy people, often with devastating consequences (Quartin et al 1997; Weycker et al 2003). Despite modern advances in critical care, one-third to half of all severely septic patients fail

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to survive to hospital discharge (Angus et al 2001; Weycker et al 2003), and those with septic shock experience even higher mortality rates (Rangel-Frausto et al 1995). Furthermore, the detrimental effects of sepsis continue beyond the acute process. Patients who survive the initial episode experience higher rates of death for the first year after hospital discharge compared with disease and age-matched controls (Weycker et al 2003).

Recent years have seen renewed enthusiasm for novel sepsis therapies, marked by an increased number of large, randomized, controlled trials. This review will discuss a few of the treatment modalities arising from these studies, including new information about recombinant human activated protein C (rhAPC), the only pharmaceutical agent approved by the US Food and Drug Administration (FDA) for the treatment of severe sepsis and septic shock. Other advances in the care of patients with septic shock, including replacement doses of corticosteroids in those with relative adrenal insufficiency and vasopressin in those with catecholamine-dependent hypotension, will also be summarized. This review will also include a discussion of a few of the provocative pharmaceutical agents with antiinflammatory and/or anticoagulant properties currently being investigated for the treatment of septic shock. Other novel agents and techniques such as macrophage migration inhibitory factor (MIF), caspase inhibitors, toll-like receptor 4 inhibitors, lipophilic antiendotoxins, extracorporeal techniques such as hemofiltration or adsorption, and fluid resuscitation strategies, are beyond the scope of this review and will not be discussed.

Sepsis pathophysiology

The systemic inflammatory response syndrome (SIRS) consists of many signs and symptoms, including tachypnea (or hypocapnea), fever, tachycardia, leukocytosis (or leukopenia), and greater than 10% immature white blood cells (Bone et al 1992; Levy, Fink, et al 2003). The presence of these signs early in the course of most septic patients fueled an initial belief that the disease resulted from an overwhelming inflammatory response to the underlying infection. Early studies demonstrated that administering endotoxin or cytokines such as tumor necrosis factor alpha (TNF- α) or interleukin-1 (IL-1) to humans resulted in an identical systemic inflammatory response syndrome with hypotension, further indicting inflammation in the pathophysiology.

Table 1: Some unsuccessful antiinflammatory treatments for septic shock in humans. All the listed antiinflammatory treatments, with the exception of replacement dose corticosteroids, have failed to demonstrate improvement in clinical outcomes in patients with septic shock

Treatments directed against:

Endotoxin (Lipopolysaccharide, [LPS])

- LPS antisera
- Murine antibodies against lipid A component of LPS
- Human antibodies against lipid A component of LPS (HA-1A)
- Bactericidal/permeability-increasing protein

Arachadonic acid metabolites

- Ibuprofen (cyclooxygenase inhibitor)
- Prostaglandin E₁
- Ketoconazole

Early cytokines

- Antitumor necrosis factor (TNF) fab dimers
- AntiTNF fab monomers
- Soluble TNF receptor fusion protein
- Murine monoclonal antiTNF antibodies
- Interleukin-1 receptor antagonist

Nonspecific antiinflammatory treatments:

- High dose corticosteroids
 - Replacement dose corticosteroids^a
 - Intravenous immunoglobulin
 - Immunonutrition
 - Platelet activating factor-acetylhydrolase
 - Tifacogin (recombinant human tissue factor pathway inhibitor)
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^a Replacement dose corticosteroids, in combination with fludrocortisone, improved survival in patients with septic shock and relative adrenal insufficiency, as defined by an inadequate response to corticotropin stimulation testing (Annane et al 2002).

More recent observations, however, indicate that coagulopathy also plays a role in sepsis pathophysiology, with microthrombi in the arterioles and venules of various organs (Levi et al 1993; Thijs et al 1993). Further investigations revealed a complex interaction between the inflammatory and coagulation systems, with inflammation stimulating procoagulant pathways, inhibiting fibrinolysis, and down-regulating other mediators controlling coagulation (van Deventer et al 1990; Esmon et al 1991, Aird 2001; Hotchkiss and Karl 2003). The resultant procoagulant state favors the formation of microthrombi in small vessels, leading to local hypoperfusion and contributing to subsequent organ dysfunction.

Initial attempts at treating septic patients focused on inhibiting mediators of the early inflammatory cascade. Although many were able to alter measures of inflammation, none were successful in improving clinical outcomes in septic patients (Zeni et al 1997; van der Poll 2001; Riedemann et al 2003; Vincent, Sun, et al 2003) (Table 1).

The reasons for these failures are heavily debated, but may include targeting the wrong inflammatory mediators, administering the treatment too late in the inflammatory course, patient heterogeneity, or a limited role for inflammation in causing organ dysfunction. The advancement of the understanding of sepsis pathophysiology to include the coagulation system, along with the availability of new agents possessing both antiinflammatory and anticoagulant properties, has renewed enthusiasm for discovering effective treatments for patients afflicted with sepsis (Matthay 2001). Unfortunately, many therapies directed against the coagulopathy associated with sepsis have also demonstrated disappointing results (Table 2).

Activated protein C

The liver, through a vitamin K-dependent pathway, synthesizes protein C and secretes it into the circulation as an inactive zymogen. Endothelial protein C receptor (EPCR), along with thrombin bound to thrombomodulin locally, facilitates the conversion of protein C to its active form. Activated protein C (APC) possesses many important physiological properties, including promoting fibrinolysis by inhibiting the release of plasminogen activator inhibitor type 1 (PAI-1) and limiting the generation of thrombin at the local site of inflammation. Equally important, APC functions as an anticoagulant by inactivating clotting factors Va and VIIIa and limits inflammation by inhibiting thrombin-induced production of inflammatory cytokines from monocytes (Esmon et al 1991). Furthermore, APC, via binding with EPCR on endothelial cells, reduces permeability injury induced by thrombin (Zeng et al 2004;

Finigan et al 2005). Similar binding of APC with EPCR on epithelial cells and white blood cells reduces apoptosis and inhibits chemotaxis, respectively (Mosnier and Griffin 2003; Nick et al 2004; Macias et al 2005). Inflammatory states, such as septic shock, impair the thrombin-thrombomodulin complex-mediated activation of Protein C and induce shedding of EPCR from cell surfaces, which increase the levels of soluble EPCR and shift the milieu to one of inflammation and coagulation. This alteration of homeostasis results in microvascular thrombi formation and organ dysfunction. Furthermore, most patients with severe sepsis have low levels of the protein C zymogen (Bernard et al 2001), and decreased levels portend worse outcomes (Yan et al 2001).

In the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, administration of exogenous rhAPC, also known as drotrecogin alfa (activated) (DAA) (Eli Lilly and Co, Inc, Indianapolis, IN, USA), significantly reduced 28 day, all-cause mortality compared with placebo in septic patients with at least one organ failure. Enrollment in this double-blind, placebo-controlled trial was terminated for efficacy after only 1690 of 2280 planned patients because the treatment group experienced a 20% relative reduction and 6% absolute reduction in mortality compared with those given placebo (24.7% vs 30.8%; $p=0.005$). The survival difference appeared shortly after initiation of the infusion, increased throughout the 28-day study period (Bernard et al 2001), and persisted into long-term follow-up (Angus et al 2003).

Who should receive APC?

Although the FDA used the results from the PROWESS study to approve DAA in November 2001 as the first drug indicated for use in severely septic patients, they limited the indication to those with a high risk of death. When dividing the enrolled patients by severity of illness scores (APACHE II [Acute Physiology and Chronic Health Evaluation II], SOFA [Sequential Organ Failure Assessment], etc), DAA produced the largest benefit in the sickest subgroups with an absolute mortality reduction of 13% (relative mortality reduction of 30%; $p=0.0002$) in patients with APACHE II scores totaling more than 24 and 7.4% (relative reduction of 19%) in patients with more than one organ dysfunction (Bernard 2003). Although not required for entry into the study, 88% of patients enrolled in the PROWESS study possessed baseline cardiovascular dysfunction, or septic shock, with 75% having sepsis-

Table 2: Elements of the coagulation homeostasis targeted as treatment for humans with septic shock. The only agent targeting coagulation homeostasis that has demonstrated a reduction in mortality to date is drotrecogin alfa (activated), which reduced 28-day all-cause mortality in patients with at least one organ dysfunction attributable to sepsis (Bernard et al 2001)

Platelets:

- Platelet activating factor receptor antagonist
- Platelet activating factor-acetylhydrolase

Protein C:

- Drotrecogin alfa (activated) (Recombinant human activated protein C)

Tissue factor

- Tifacogin (recombinant human tissue factor pathway inhibitor)

Antithrombin III

- High dose antithrombin III

induced dysfunction of at least two organ systems. The relatively limited number of patients with less severe sepsis made it difficult to reach conclusions about the effects of DAA in such patients. A subsequent trial was undertaken to evaluate the effect of rhAPC on these septic patients with only a single organ dysfunction. The Administration of Drotrecogin Alfa (activated) in Early Severe Sepsis (ADDRESS) trial was stopped after an interim analysis of an initial 2640 of the 11 000 targeted patients due to a low likelihood of demonstrating a significant mortality benefit for such low risk patients (Abraham et al 2005). The recently published data demonstrated similar 28-day (18.5% vs 17%; $p=0.38$) and in-hospital (20.6% vs 20.5%) all-cause mortality rates for patients treated with either rhAPC compared with placebo. Similarly, a randomized, double-blind, placebo controlled study of drotrecogin alfa (activated) in children with severe sepsis was also terminated early after 400 patients as the data safety and monitoring board concluded DAA was highly unlikely to show improvement in time to resolution of organ failure compared with placebo (DHP 2005). All-cause, 28-day mortality rates, although slightly lower than those seen in adults enrolled in the PROWESS and ADDRESS trials, also did not differ between treatment groups (17% vs 18%).

The subgroups of septic patients for which DAA treatment is the most beneficial continues to be hotly debated (Ely et al 2002; Warren et al 2002). In the PROWESS trial, rhAPC decreased mortality rates compared with placebo consistently across all demographic subgroups defined by age, sex, and race (Bernard et al 2001; Bernard 2003), as well as across different underlying disease states including cancer, chronic obstructive pulmonary disease, and preexisting congestive heart failure (Bernard et al 2001). Furthermore, DAA treatment resulted in a consistent reduction in mortality for different types (gram-positive, gram-negative, mixed, or fungus), and sites of infection (Bernard et al 2001), with the exception of urinary tract infections, where limited data prevented definitive conclusions. Only 27% of patients enrolled in the PROWESS trial were postoperative from either elective or emergency surgery, which limits conclusions about the efficacy of DAA in these patients. Considerably more postoperative patients ($n=1002$) were enrolled in the ADDRESS trial, which demonstrated that postoperative patients with only a single organ dysfunction experienced significantly higher 28-day mortality rates (20.7% vs 14.1%; $p=0.03$) and numerically higher in-hospital mortality rates

when administered DAA compared with those given placebo (23.4% vs 19.7%; $p=0.26$) (Abraham et al 2005). Although the primary cause of death in this population was sepsis-related, postoperative patients treated with rhAPC experienced significantly more bleeding events than those treated with placebo. Of the surgical patients who had a bleeding episode, more patients treated with rhAPC than placebo died of sepsis-induced multiorgan dysfunction or hemorrhage (Abraham et al 2005).

Aside from severity of illness, measured by number of organ failures, identifying baseline prognostic indicators has proven difficult. Data from over 1000 severely septic patients receiving placebo in multiple, randomized, phase III trials demonstrated that patients who either develop new or fail to improve existing organ dysfunctions over the initial 24 hours of severe sepsis experience significantly higher morbidity and mortality, even after correcting for severity of illness (Levy, Macias, et al 2003; Vincent, Sundin, et al 2003). Although the development of septic shock and cardiovascular collapse is frequently recognized as a poor prognostic indicator, evidence now establishes that failing to improve or worsening shock over the same time period also confers significant mortality. Unfortunately, it remains problematic to determine which patients are likely to improve over the first 24 hours. Additional indicators of outcome will become more clear as investigations into prognostic factors such as B-type natriuretic peptide (BNP) and procalcitonin continue. Numerous studies have demonstrated that elevated levels of procalcitonin are a sensitive marker for sepsis (Assicot et al 1993; Ugarte et al 1999; Aikawa et al 2005), and that higher levels portend worse prognosis (Clec'h et al 2004). Likewise, higher levels of BNP in patients with septic shock have also been shown to correlate with worse outcomes (Witthaut et al 2003; Brueckmann et al 2005). Furthermore, treatment with rhAPC lowered BNP levels and was associated with improved outcomes (Brueckmann et al 2005). Future studies will need to be undertaken to determine if these, or other similar sepsis markers, can be used to direct sepsis therapies to those patients most likely to benefit or if these markers can be used to evaluate effectiveness of treatment.

Timing of APC administration

Early treatment of septic shock is vitally important for minimizing morbidity and mortality. For many years, cardiologists and neurologists have emphasized that "time is heart" and "time is brain" in the treatment of myocardial

infarction and stroke, respectively. In patients with severe sepsis, “time is tissue.” Rivers et al (2001) demonstrated that goal-directed resuscitation in the initial 6 hours of septic shock reduced 28-day, all-cause mortality. Goal-directed resuscitation did not decrease mortality during the 6 hour resuscitation period, but patients who received this therapy experienced considerably less sudden cardiac death in the days after the resuscitation period. Likewise, evidence suggests that early administration of appropriate antibiotics reduces mortality in septic patients (Ibrahim et al 2000).

Similar administration timing data have been accumulated for rhAPC. Post-marketing analysis of patients receiving DAA provides evidence that administration within 24 hours of initial organ dysfunction decreases mortality. In a retrospective review of rhAPC-treated patients from 5 academic medical centers, early administration of DAA was associated with reduced mortality (Odds Ratio [OR] 0.52; 95% Confidence Interval [CI]: 0.45–0.60), even after controlling for age, other organ dysfunctions, mechanical ventilation, and vasopressor use (Wheeler, Steingrub, et al 2003). In the PROWESS trial, the majority of patients received rhAPC within 24 hours of meeting severe sepsis criteria, with a 17–18 hour average time to initiation of DAA (Bernard et al 2001). However, retrospective analysis demonstrates that post-marketing administration occurs significantly later in the disease course, starting an average of 2.3 days after the onset of severe sepsis (Schmidt et al 2003). Earlier administration improved outcome, with 33% mortality in patients beginning the infusion on the same day they developed their initial sepsis-related organ dysfunction, compared with 40% in those commencing the day after, and 52% in patients starting after the second day of organ dysfunction ($p=0.05$) (Wheeler, Steingrub, et al 2003). Furthermore, a prospective, phase IIIb study of 2378 patients treated with DAA found mortality rates of 33% when DAA was initiated on the same calendar day as developing severe sepsis compared with 41% for those treated after the first day ($p=0.02$) (Wheeler, Doig, et al 2003). Regression analysis, using an integrated database of over 4400 patients treated with either rhAPC or placebo up to 72 hours after the development of organ dysfunction from 5 separate severe sepsis studies, found a relative risk of death for patients treated at the onset of organ dysfunction of 0.67, compared with 0.76 and 0.88 for those treated 12 and 24 hours later, respectively (Vincent, Sundin, et al 2003). The time from development of organ dysfunction to treatment with DAA in the recently stopped ADDRESS trial averaged

48 hours, which caused many to speculate that delayed treatment reduces effectiveness (Abraham et al 2005). Whether a time point exists in the course of severe sepsis after which DAA is no longer effective remains unknown. However, administration early in the course clearly improves survival, and delaying administration, even by as little as a few hours, increases mortality.

Likewise, it remains unknown whether longer treatment would benefit subgroups of severely septic patients. Although rhAPC was administered for a total of 96 hours in the PROWESS study, many physicians believe that extended treatment is warranted for patients who continue to manifest organ dysfunction. An ongoing study (EXTEND [A Phase IIIb Study to Determine Efficacy and Safety of Extended Drotrecogin Alfa (Activated) Therapy in Patients With Persistent Requirement for Vasopressor Support After 96 Hour Infusion With Commercial Drotrecogin Alfa (Activated)]) is investigating whether continuation of DAA longer than 96 hours is beneficial in septic shock patients with continued cardiovascular compromise.

APC and bleeding

Treatment with rhAPC is not without risk. Despite excluding patients at high risk of bleeding (ie, multiple traumatic injuries, initial platelet count below 30 000/mL, liver failure) from enrollment in both the PROWESS and ADDRESS trials, treatment with DAA increased the risk of bleeding compared with placebo. The incidence of serious bleeding, defined as any intracranial hemorrhage, life-threatening bleed, or blood loss requiring transfusion of more than 3 units of packed red blood cells on 2 consecutive days, was almost twice as high when DAA was administered (3.5% vs 2.0% in PROWESS; $p=0.06$; and 3.9% vs 2.2% in ADDRESS; $p=0.01$) (Bernard et al 2001; Abraham et al 2005). Patients with either traumatic injuries of highly vascular organs or blood vessels, markedly abnormal pretreatment coagulation parameters, or ulcerations of the gastrointestinal tract, experienced most of the serious bleeding episodes (Bernard et al 2001, 2003). Not surprisingly, these bleeding rates compare similarly with those seen with other forms of full-dose, systemic anticoagulation, such as unfractionated or low-molecular weight heparin for the treatment of pulmonary embolus or myocardial infarction (Dolovich et al 2000). In addition, serious bleeding rates did not increase when subcutaneous low-molecular-weight or unfractionated heparin (up to 15 000 units per day) were administered concomitantly with

rhAPC to prevent deep vein thromboses (3.7% with heparin vs 3.5% without) (Bernard et al 2001). The risk of bleeding when rhAPC is administered concomitantly with prophylactic unfractionated and low-molecular-weight heparin is being further evaluated in an ongoing prospective, randomized study (Lilly EVBR Study). The increased risk of severe bleeding was found to be limited to the peri-infusion period (ie, duration of the infusion plus an additional 24 hours). Upon completion of the infusion, bleeding rates in patients treated with DAA were identical to those given placebo (Siegel 2002). Fortunately, rhAPC is rapidly degraded by serum proteases, yielding a half-life of minutes, regardless of renal or hepatic function. This allows many of these bleeding episodes to be effectively managed by merely discontinuing the infusion.

Particular concern has arisen over the risk of intracranial hemorrhage with the use of APC. Analysis of almost 3000 patients treated with rhAPC, including those in open-label trials, found the incidence to be 0.6%, with most events occurring in patients suffering meningitis, platelet counts less than 30 000/ μ L, or both (Ely et al 2002; Bernard et al 2003). Less severely ill patients experienced similar rates of CNS bleeding in the ADDRESS trial (0.5% DAA vs 0.4% placebo) (Abraham et al 2005). Unfortunately, CNS bleeding may occur more frequently in children treated with DAA. In the randomized, placebo-controlled trial of severely septic children, 4 patients (2%) treated with DAA had CNS hemorrhages compared with 1 (0.5%) in the placebo arm. Three of the 4 intracranial bleeds associated with DAA treatment occurred in children less than 60 days old (DHP 2005).

Promising treatments for the future of septic shock: anticoagulants with antiinflammatory properties

Recent advances in the complex pathophysiology of sepsis have illuminated the delicate homeostasis in which the inflammatory and coagulation systems coexist. The overwhelming early inflammation during septic shock alters this tenuous balance and initiates a cascade of events that result in a highly proinflammatory and procoagulant environment. In this environment, inflammation and coagulation act in concert and augment each other, with both playing a role in the morbidity and mortality associated with septic shock. The recently discovered success of APC, with its ability to interrupt both the inflammatory and

coagulation cascades simultaneously, has spurred further investigations into additional agents, which similarly possess both antiinflammatory and anticoagulant properties.

Heparin

Heparin binds antithrombin III to form a complex capable of inhibiting thrombin. This inhibition helps prevent clot formation, and has allowed glycosaminoglycan to be utilized clinically as an anticoagulant for more than 60 years. More recent data, however, demonstrate that heparin also possesses antiinflammatory properties. P- and L-selectins are expressed locally at inflammation sites. These endothelial cell surface markers play an important role in attracting leukocytes and allowing them to infiltrate into the inflamed tissue. Heparin, by blocking these P- and L-selectins, impedes leukocyte adhesion to the endothelium and prevents infiltration into tissue (Want et al 2002). In addition, heparin inhibits TNF- α , a key component in the inflammatory cascade. Heparin also inhibits complement activation and platelet activating factor, two mediators that propagate the proinflammatory and procoagulant cycle of septic shock (Tyrell et al 1999). Since the only approved treatment for septic shock, namely APC, possesses both antiinflammatory and anticoagulant properties, many have hypothesized that heparin might also be effective in the treatment of sepsis and at a considerably lower cost compared with novel medicines.

The use of heparin to prevent deep vein thrombosis in patients with severe sepsis randomized to receive placebo in therapeutic trials of other agents provides some preliminary data on its possible efficacy in these patients. Patients who received prophylactic dosages of unfractionated or low-molecular weight heparin experienced reduced mortality rates compared with patients given placebo without heparin (Davidson et al 2002; Langer et al 2002). This association, however, must be interpreted with caution due to the possibility of indication bias. In other words, the decision to administer heparin to these patients is left to the discretion of the treating medical team and not randomized. Other clinical considerations, such as the presence or absence of disseminated intravascular coagulation or increased bleeding risk, strongly influence the clinicians' decision to prescribe heparin. As such, patients with severe sepsis who are chosen to receive heparin prophylaxis are almost assuredly different than those not chosen to receive it.

Unfortunately, quality data on the effectiveness of heparin in the treatment of severe sepsis are sparse. Even data on its effectiveness in animal models of severe sepsis

or septic shock are lacking. Furthermore, preclinical data on the optimal dose, timing, and duration of treatment is similarly unavailable and randomized or placebo-controlled studies in humans have not been conducted. With its known significant risks of hemorrhage and heparin-induced thrombocytopenia, the paucity of animal and early clinical data will need to be overcome prior to advancing to large, definitive studies in severely septic humans. Until additional data is generated, including that from randomized controlled trials in humans, the effectiveness and safety of heparin in treating severe sepsis will remain unknown.

Tissue factor inhibitors

Tissue factor (TF) is an important transmembrane glycoprotein mediator of both the coagulation and inflammatory cascades. Normally, TF is expressed in the subendothelial cells of the vascular adventitia (Eilertsen and Osterud 2004). In this location, TF is protected from exposure to the systemic circulation (Morrissey et al 1993). Proinflammatory cytokines, such as TNF- and IL-1, induce endothelial cells to express TF (Meszaros et al 1994). When expressed on endothelial cells, TF is exposed to the circulation where it can bind with circulating activated factor VII and initiate the coagulation cascade (Osterud and Rapaport 1977). Likewise, coagulation factors generated by TF-initiated coagulation, like activated factor VII, activated factor X, and thrombin, elicit inflammatory responses by attracting neutrophils and stimulating the release of cytokines from macrophages and endothelial cells (Esmon et al 1991). Localized activation of the coagulation cascade associated with inflammation helps control the spread of infectious agents. In severe sepsis, however, TF expression often spreads beyond the local site of inflammation, resulting in a diffuse, prothrombotic state similar to disseminated intravascular coagulopathy (Cressey 2000). This coagulopathic state further propagates inflammation (Warr et al 1990). The end result is an accelerated cycle of coagulation and inflammation that results in endothelial dysfunction and end-organ damage.

Antagonism of TF, either through TF pathway inhibitor (TFPI) (Creasey et al 1993) or anti-TF antibodies (Taylor et al 1991) in nonhuman primate models of sepsis, reduces both inflammation and coagulation and improves mortality. TFPI is a naturally occurring protein that functions in maintaining coagulation homeostasis. Like heparin, TFPI possesses both anticoagulant and antiinflammatory properties. In its active, untruncated form, TFPI inhibits TF and decreases the formation of thrombin. TFPI is truncated,

however, in many procoagulant states, such as sepsis. This truncation decreases its anticoagulant activity (Wesselschmidt 1993), which ultimately shifts homeostasis towards coagulation, predisposing patients to form microthrombi.

Many experts enthusiastically embraced the concept of inhibiting TF, either through TFPI or anti-TF antibodies, as a means of treating severe sepsis, because of the dual role that TF plays in accelerating both inflammation and coagulation. Unfortunately, the recently completed multicenter, randomized, blinded phase 3 trial of recombinant exogenous TFPI demonstrated no mortality benefit in severely septic patients (n=880) compared with placebo (n=874) (Abraham et al 2003). Although the overall results were discouraging, a closer look at the study data has renewed enthusiasm for TF antagonism. In the early phase of the trial, prior to large changes in mortality rates, the data suggested a benefit from TFPI administration. Furthermore, TFPI appeared to decrease mortality in the subgroup of patients with normal international normalized ratios (INR) < 1.2. Consequently, further studies investigating the effectiveness of TFPI in subgroups of patients with severe sepsis are planned. In addition, investigations into the safety and effectiveness of anti-TF antibodies in treating patients with severe sepsis and pulmonary dysfunction are currently in the early stages of clinical trials.

Treatments for subgroups of patients with septic shock

Vasopressin or antidiuretic hormone

Vasopressin, a protein produced in the hypothalamus (Swaab et al 1975), stored in the posterior pituitary, and released into the circulation in response to many complex stimuli (Schrier et al 1979; Wood and Chen 1989), produces a wide range of physiologic effects, including maintaining blood pressure homeostasis (Reid and Schwartz 1984). Also known as antidiuretic hormone (ADH), vasopressin restores vascular tone in patients with distributory shock via a number of mechanisms. Acting through vascular V_1 -receptors, the endogenous hormone directly induces vasoconstriction (Reid and Schwartz 1984). In addition, ADH also modulates potassium-adenosine triphosphate (ATP) channels and nitric oxide synthesis. Furthermore, vasopressin potentiates the adrenergic effects of other vasoconstrictor agents (Landry and Oliver 2001). Although vital in elevating low blood pressure, especially when it is the result of inappropriate vasodilation, vasopressin does

not significantly alter vascular smooth muscle constriction in humans with normal blood pressure (Graybiel and Glendy 1941; Wagner and Braunwald 1956; Schwartz et al 1983). Vasopressin also has varying effects in different tissues. In nonvital arterial systems which feed skeletal muscles, fat, and skin, vasopressin results in potent vasoconstriction, but causes considerably less vasoconstriction in the coronary, mesenteric, and cerebral circulations (Laszlo et al 1991).

Kinetics of serum vasopressin levels in septic shock patients

Hypotension, hypovolemia, and elevated serum osmolality are the most potent stimuli for the release of vasopressin from the posterior pituitary (Schrier et al 1979; Quail et al 1987; Norsk et al 1993). Despite the potency of the stimulus, only 10%–20% of the vasopressin stored in the posterior pituitary is available for immediate release. Subsequent release of vasopressin occurs at a much slower rate, resulting in a biphasic response (Holmes, Patel, et al 2001; Sharshar et al 2003). In the early phase of distributive states, such as septic shock, serum ADH levels rise appropriately as the posterior pituitary rapidly secretes the 10%–20% of its available stores to maintain organ perfusion. As vasodilatation continues, serum concentrations begin to fall, ultimately leading to inadequate levels of vasopressin within 36 hours in patients with persistent vasodilatation and distributive shock (Sharshar et al 2003). Although the exact mechanism for these falling levels remains an enigma, it appears to occur through decreased hypothalamic production and/or release of pituitary stores and not via increased catabolism, as levels increase appropriately when exogenous vasopressin is given (Bourque and Oliet 1997).

Although vasopressin has relatively little effect on blood pressure in humans without hypotension, low blood pressure from vasodilatation results in an increased sensitivity to the vasoconstrictive effects of vasopressin (Landry et al 1997a). Consequently, its administration in relatively low replacement doses in this condition significantly increases arterial blood pressure. Unfortunately, the optimal dose of vasopressin for treatment of septic shock remains unknown. In animal models, limited data suggest that continuous infusion of low doses produces vasoconstriction only in selective arterial systems, with carotid blood flow actually increasing without compromising blood flow to other vital organs (Malay et al 2004). Moderately higher doses likely result in more potent vasoconstriction in arterial vascular beds and may induce mesenteric, renal, or coronary ischemia. Two recent human studies have demonstrated

increased gastric regional production of carbon dioxide upon administration of vasopressin, suggesting compromised gut blood flow (Klinzing et al 2003; van Haren et al 2003). The combination of the animal and human data has led many experts to recommend a continuous infusion of vasopressin only as a supplement to other vasoactive agents and at a low dose (0.01–0.04 Units/minute [U/min]) without titrating higher if blood pressure remains inadequate (Dellinger et al 2004; Malay et al 2004; Holmes and Walley 2004).

Clinical studies of vasopressin in septic shock

Landry and colleagues (1997b) found markedly lower serum vasopressin in patients with established septic shock requiring catecholamines compared with those with cardiogenic shock needing catecholamines (3.1 pg/mL vs 22.7 pg/mL, $p < 0.001$). They then supplemented the inadequate endogenous levels with low, physiologic doses of exogenous vasopressin in these septic shock patients and discovered a significant improvement in arterial blood pressure, further confirming the contributory role of inadequate vasopressin levels to this state of distributive shock. Exogenous supplementation of vasopressin in these patients produced a marked increase in systemic vascular resistance and a slight decrease in cardiac output, which suggests vasoconstriction as the mechanism of increasing arterial blood pressure. Subsequent studies have confirmed the association of inadequate levels of vasopressin with vasodilatory shock (Argenziano et al 1997, 1998; Sharshar et al 2003).

Although numerous studies have investigated supplementing inadequate endogenous levels with relatively low doses (0.01–0.1 U/min) of exogenous vasopressin in patients with catecholamine-dependent septic shock, most have done so through open-labeled use of the drug (Table 3). Furthermore, these studies fail to evaluate the effect of these replacement doses of vasopressin on clinically important outcomes such as mortality, renal failure, or ICU, or hospital length of stay. Instead, the studies utilize surrogate endpoints as evidence of efficacy such as increased blood pressure, increased peripheral vascular resistance, and decreased or abolished need for catecholamine support.

Vasopressin may possess other beneficial effects in patients with septic shock. Prospective open-labeled studies have demonstrated increased urine output with exogenous vasopressin administration (Landry et al 1997a; Tsuneyoshi et al 2001), supporting the findings of a few retrospective studies (Gold et al 2000a, 2000b; Holmes, Walley, et al 2001). Unfortunately, the mechanism of this increased urine

Table 3: Studies of vasopressin in humans with septic shock. A conglomeration of studies investigating the effects of vasopressin (antidiuretic hormone; [ADH]) in humans with septic shock

Reference	Design	Patient Population/disease	Number of patients	Comparison	Vasopressin	
					Dose Units/minutes	Outcomes
Landry et al 1997b	Prospective, open-label, unrandomized	Septic shock on catecholamines	10	Pre- vs Post-ADH	0.04 U/min	↑ BP
Landry et al 1997b	Prospective, open-label, unrandomized	Septic shock on catecholamines	6	Pre- vs Post-ADH	0.01 U/min	↑ BP
Landry et al 1997b	Prospective, open-label, unrandomized, removal of ADH	Septic shock on catecholamines	6	On ADH vs Post-stopping ADH	0.01 U/min	↓ BP on removal of ADH
Landry et al 1997a	Prospective, open-label, unrandomized case reports	Septic shock on catecholamines	5	Pre- vs Post-ADH	0.03–0.04 U/min	↑ BP, ↓ Cat, ↑ UO
Malay et al 1999	Prospective, randomized, placebo-controlled, double-blinded	Trauma patients with septic shock on catecholamines	10	ADH (n = 5) vs Placebo (n = 5)	0.04 U/min	↑ BP, ↓ NE
Dunser et al 2001	Retrospective	Septic (n = 35) or post-cardiotomy shock (n = 25) on catecholamines	60	Pre- vs Post-ADH	0.07–0.1 U/min	↑ BP, ↓ NE, ↓ HR, ↓ CI, ↓ mean PAP, ↑ liver enzymes, ↓ plt
Holmes, Walley, et al 2001	Retrospective	Septic shock on catecholamines	50	Pre- vs Post-ADH	0.01–0.6 U/min (avg. 0.5 U/min)	↑ BP, ↓ Cat, ↑ UO, ↓ CI
Tsuneyoshi et al 2001	Prospective, open-label	Septic shock on catecholamines	16	Pre- vs Post-ADH	0.04 U/min	↑ BP, ↑ UO
Patel et al 2002	Prospective, randomized, blinded	Septic shock	24	ADH (n = 13) vs NE (n = 11)	0.01 U/min titrated up to 0.08 U/min	↑ BP, ↓ NE, ↑ UO, ↑ CCI
Dunser et al 2003	Prospective, randomized, blinded	Cardiopulmonary bypass ± septic shock	48	NE + ADH (n = 24) vs NE alone (n = 24)	0.067 U/min	↑ BP ↓ tachyarrhythmias

Abbreviations: ADH, antidiuretic hormone; BP, blood pressure; Cat, catecholamines; CCI, creatinine clearance; CI, cardiac index; HR, heart rate; NE, norepinephrine; PAP, pulmonary artery pressure; plt, platelets; PVR, peripheral vascular resistance; SVR, systemic vascular resistance; U/min, units/minute; UO, urinary output.

flow remains ill-defined and may simply be the result of improved renal perfusion through increased arterial blood pressure.

Only a limited number of prospective, randomized, blinded studies have compared the effects of vasopressin supplementation with either placebo or another vasopressor (Argenziano et al 1997; Malay et al 1999; Patel et al 2002). Although these studies provide objective evidence that vasopressin can improve short-term surrogate outcomes such as increasing mean arterial pressure or reducing catecholamine doses, data that vasopressin administration improves patient mortality, intensive care, or hospital lengths of stay, or other long-term clinical outcomes, is still lacking. A large, multicenter, randomized, double-blinded, placebo-controlled Vasopressin and Septic Shock Trial (VASST) is currently underway to compare the effects of vasopressin on long-term clinical outcomes, including mortality, renal function, and lengths of stay in patients with catecholamine-dependent septic shock (Cooper et al 2003). Until data from

this study are available, vasopressin should probably continue to be reserved as a “rescue” vasopressor agent to be given in low, physiologic doses (0.04 U/min) only to patients unable to maintain an adequate blood pressure despite the use of continuous catecholamine support.

Corticosteroid replacement therapy

The antiinflammatory properties of corticosteroids include inhibition of proinflammatory cytokine production, enhancement of antiinflammatory mediator release, and reduction in both the function and migration of inflammatory cells, such as lymphocytes, monocytes, neutrophils, macrophages, and eosinophils. Because of these numerous antiinflammatory effects, many investigators labeled corticosteroids as the ideal antidote for the presumptive overwhelming inflammatory response in sepsis. Unfortunately, high dose corticosteroids administered to septic patients repeatedly failed to demonstrate clinical benefit. Furthermore, meta-analyses confirmed the lack of

efficacy and even suggested a trend toward harm (Cronin et al 1995; Lefering and Neugebauer 1995; Zeni et al 1997).

Recent data demonstrate that lower doses of corticosteroids, administered over a longer period of time, may benefit at least one subset of patients with septic shock. Many patients with refractory septic shock have relative adrenal insufficiency, lacking adequate adrenal function to produce an appropriate cortisol response for their level of illness (Annane et al 2000). Current data now suggest that moderate doses of corticosteroids, considerably smaller than those previously found to be ineffective, may prove beneficial in these septic shock patients with relative adrenal insufficiency.

A recent double-blinded, multicenter trial randomized 299 French patients with septic shock of less than 8 hours duration to receive 7 days of either placebo or 50mg of intravenous hydrocortisone every 6 hours plus 50mg of fludrocortisone via nasogastric tube each day (Annane et al 2002). Although corticotropin stimulation tests were performed in all patients prior to administration of study medications, the test results remained unknown to the investigators and treating physicians until completion of the study. Administration of replacement dose corticosteroids improved refractory hypotension and decreased absolute mortality by 10% as compared with placebo (63% vs 73% mortality; $p=0.02$), but only in the subgroup of septic shock patients found to have relative adrenal insufficiency. For the purposes of this study, relative adrenal insufficiency (or “nonresponders”) was defined by a failure to increase serum cortisol levels by greater than 9 mcg/dL within 2 hours of the corticotropin stimulation test (Annane et al 2002). Unfortunately, only the “nonresponding” subgroup demonstrated benefit. In fact, for the relatively small subset of septic shock patients classified as “responders”, or those who increased their serum cortisol concentrations by greater than 9 mcg/dL in response to adrenocorticotropin hormone, treatment with even these moderate replacement doses of corticosteroids produced a trend toward increased mortality (53% vs 61%) (Annane et al 2002). This has led many physicians to perform a cortisol stimulation test in septic shock patients and immediately initiate steroid replacement therapy while awaiting the results. If the patient is found to have an inadequate cortisol response, steroids are continued, and if the cortisol level rises appropriately, the steroids are discontinued (Dellinger et al 2004).

Other recently completed studies have shown similar improvements in hypotension and mortality in septic shock patients treated with more moderate corticosteroid dosages

(Bollaert et al 1998; Briegel et al 1999), suggesting that at least some subgroups of septic patients benefit from these lower and more prolonged doses of corticosteroids. Debate continues over the exact definition of adrenal dysfunction, the length of steroid treatment after resolution of shock, whether steroids should be tapered, and the need for fludrocortisone as part of the treatment (Cooper and Stewart 2003). Hopefully, the ongoing multicenter, international CORTICUS (Corticosteroid Therapy of Septic Shock Trial) study, which randomizes catecholamine-dependent septic shock patients to replacement dose steroids or placebo until resolution of shock, will help clarify many of these issues (Annane et al 2003).

Promising treatments for the future of septic shock: antiinflammatory agents

Despite an improved understanding of the delicate homeostasis between the inflammatory and coagulation systems, evidence suggests that the cascade of events in sepsis is initiated by a release of inflammatory mediators. These mediators result in the clinical signs and symptoms of sepsis. If allowed to propagate without close regulation, these mediators contribute to tissue damage. Consequently, even in the face of numerous previously unsuccessful phase III trials in humans, inhibiting the initial inflammatory reaction continues to be a focus of new pharmaceutical development.

High-mobility group box 1 protein

Despite promising animal and phase II data, treatments directed against early mediators of inflammation, such as TNF, IL-1 receptor, or endotoxin (lipopolysaccharide [LPS]) have failed to demonstrate benefit in improving clinical outcomes in patients with severe sepsis or septic shock (Table 1). Many experts surmise that initiation of these agents occurred too late in the inflammatory course to inhibit its numerous effects, leading to the disappointing results. Unfortunately, most patients do not present to a medical care facility until they experience the signs or symptoms associated with sepsis. Since the inflammatory reaction is responsible for producing these early symptoms, the detrimental inflammatory cascade is already well underway at the time of presentation. Furthermore, many deaths from sepsis occur later in the course, at least 48–72 hours after the onset of symptoms, prompting many to speculate that therapy directed against inflammatory mediators with

prolonged actions or which appear later in the course might prove more successful.

High-mobility group box protein 1 (HMGB1) may represent one such late mediator. This 30kDa protein was purified along with histones from nuclei almost three decades ago (Goodwin and Jones 1977). Named for their rapid migration on electrophoretic gels, high mobility group nuclear proteins have been classified as nonhistone chromatin-associated proteins. The nuclear binding properties of HMGB1, along with its critical role in gene transcription, DNA repair and replication have been extensively studied since its discovery (Einck and Bustin 1985; Bianchi and Beltrame 1988; Bianchi et al 1989). Recent data suggest that HMGB1 also possesses inflammatory properties (Andersson et al 2000). Although it was discovered because of its association with chromatin, HMGB1 only binds DNA nonspecifically and with low affinity, allowing movement from the nucleus to the cytosol through nuclear pores (Falciola et al 1997). Acetylation in the cytosol prevents nuclear re-entry and allows for extracellular secretion (Bonaldi et al 2003). Cultured macrophages secrete HMGB1, in the absence of cell death, in response to stimulation from LPS, gamma interferon, or TNF (Wang et al 1999; Andersson et al 2000; Rendon-Mitchell et al 2003; Chen et al 2004). In addition, HMGB1 is passively released from all nucleated cells upon cell necrosis, but not apoptosis (Scaffidi et al 2002; Harris and Andersson 2004).

Once extracellular, HMGB1 functions as an important inflammatory mediator. Extracellular HMGB1 fuels inflammation by stimulating the release of additional proinflammatory cytokines from endothelial cells and monocytes, including TNF- α , IL-1, IL-6, IL-8, and macrophage inflammatory protein. Furthermore, HMGB1 also helps regulate coagulation by inducing the expression of adhesion molecules in endothelial cells, resulting in the secretion of plasminogen activator inhibitor-1 and tissue plasminogen activator (Fiuza et al 2003; Treutiger et al 2003). Mice develop markedly elevated levels of serum HMGB1 when administered LPS (Wang et al 1999; Yang et al 2004). However, unlike many classic inflammatory mediators that peak early in the course of sepsis and become undetectable within a few hours, serum levels of HMGB1 remain undetectable until 8 hours after the onset of sepsis and continue to increase until reaching a plateau at 24 to 32 hours after sepsis onset (Wang et al 1999; Sundén-Cullberg et al 2005). Administration of recombinant HMGB1 provides further evidence for its role in sepsis. Mice

treated with sublethal doses of HMGB1 develop signs of endotoxemia within 2 hours (Wang et al 1999). Higher doses result in death at 18–36 hours, even in mice resistant to the effects of LPS, indicating that HMGB1 is toxic even in the absence of other mediators of LPS-induced inflammation (Wang et al 1999). Intratracheal administration of HMGB1 in mice produces neutrophilic lung infiltration and edema, an alveolitis picture consistent with the acute lung injury seen in severe sepsis, within about 8 hours and continuing through 24 hours (Abraham et al 2000).

Patients with severe sepsis and septic shock also have elevated serum levels of HMGB1 compared with undetectable levels in healthy controls (Wang et al 1999; Sundén-Cullberg et al 2005). These elevated levels arise from both discharge from necrotic cells along with the production and release of HMGB1 from macrophages, stimulated by exogenous bacterial LPS and endogenous proinflammatory cytokines. In addition, one study found a prognostic implication for serum HMGB1 levels, as nonsurviving septic patients demonstrated considerably higher levels than those who survived to hospital discharge (Wang et al 1999). A recent study has also confirmed the presence of elevated levels of HMGB1 in plasma and bronchoalveolar lavage in septic patients with acute lung injury (Yang et al 2004). Although HMGB1 was present in similarly low levels in bronchoalveolar lavage fluid from healthy adults and at the onset of disease in those with sepsis, peak levels were 2–4 times higher during the course of lung injury.

Blocking the effects of HMGB1, even well after signs of sepsis develop, improves survival in multiple animal models (Ulloa et al 2002; Yang et al 2004). Anti-HMGB1 antibodies, when given both before and after LPS instillation, protect mice from the lethal effects of endotoxin (Wang et al 1999). Importantly, treatment with these antibodies did not just extend the time to death, but actually allowed many of the mice to survive until necropsy at 2 weeks. Likewise, anti-HMGB1 antibodies, given to mice 24 hours after cecal perforation, decreased mortality compared with immunoglobulin-G (IgG)-treated controls (72% vs 28%; $p < 0.03$), and even “rescued” animals already exhibiting signs of severe sepsis (Yang et al 2004). Ethyl pyruvate, a nontoxic food derivative, blocks the effects of HMGB1 by inhibiting its release from LPS- and TNF-stimulated macrophages (Ulloa et al 2002). Treatment with ethyl pyruvate conferred similar mortality and end-organ damage protection even when given to mice 24 hours after endotoxin challenge (Ulloa et al 2002).

The HMGB1 protein has 3 distinct domains: 2 DNA binding elements, called A-Box and B-box, and a negatively charged C terminal. The cytokine activity of HMGB1 localizes to 20 amino acids found in the B-box DNA binding domain (Li et al 2003). The A-box DNA binding site competes with HMGB1 for binding sites on the surface of macrophages and attenuates the release of TNF and IL-1 (Yang et al 2004). Administration of A-box peptide reduces mortality in mice, even when administered up to 24 hours after cecal ligation and puncture, providing further evidence that HMGB1 antagonism may improve outcomes in sepsis.

The efficacy and safety of inhibiting HMGB1 in humans with sepsis has not yet been demonstrated. However, the encouraging results of HMGB1 inhibition in animal models, combined with its “prolonged therapeutic window” have brought enthusiasm for its use as a possible future intervention for patients with severe sepsis or septic shock. It remains unknown whether this inhibition is best accomplished via antibodies, inhibitors like ethyl pyruvate, or antagonists such as A-box peptide.

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins)

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, were originally developed for reducing serum cholesterol levels. Subsequent investigations demonstrated that they also reduced morbidity and all-cause mortality in patients with cardio- or cerebrovascular disease, including a reduction in non-coronary mortality (Packard 1998). Research into the mechanism for this benefit found that these medications possess immunomodulatory effects independent of their lipid lowering abilities.

As described above, endothelial dysfunction is a major contributor to both the proinflammatory, procoagulant, and antifibrinolytic cascades that occur in severe sepsis. Many of the pleiotropic effects of statins are thought to be related to their ability to prevent endothelial dysfunction and enhance endothelial fibrinolytic and anticoagulant properties (Takemoto and Liao 2001). Statins increase the expression and enhance the activity of endothelial nitric oxide synthase (eNOS) (Laufs et al 1998). Data also demonstrate that statins restore eNOS activity in the presence of hypoxia (Laufs et al 1997), which is often the condition of tissue capillaries in septic shock. Endothelium-derived nitric oxide, produced from eNOS, promotes vascular relaxation (Ignarro et al 1987), suppresses aggregation of platelets on the

endothelium (Radomski et al 1992), and inhibits endothelium–leukocyte interactions (Kubes et al 1991). HMG-CoA reductase inhibitors also possess other properties that promote healthy endothelial function, including the ability to upregulate tissue plasminogen activator (Essig et al 1998), downregulate plasminogen activator inhibitor, decrease the expression of TF (Aikawa et al 2001), and reduce oxidative stress (Rikitake et al 2001). Additionally, statins reduce vascular inflammation by reducing endothelial cell expression of adhesion molecules, which further suppresses the ability of leukocytes to attach to the endothelium (Gauthier et al 1995; Niwa et al 1996).

Statins also possess antiinflammatory properties that may prove beneficial in attenuating the inflammatory cascade found in severe sepsis. Data demonstrate that HMG-CoA reductase inhibitors impede the migration of inflammatory cells (Dunzendorfer et al 1997) and inhibit neutrophil chemotaxis (Kreuzer et al 1991). Furthermore, statins suppress macrophage growth (Sakai et al 1997) and inhibit the production and secretion of proinflammatory cytokines, including TNF, IL-1, IL-6, and IL-8, from macrophages and endothelial cells (Pahan et al 1997; Kothe et al 2000).

Animal data further suggest a role for statins in treating severe sepsis. Mice, pretreated with intraperitoneal injection of simvastatin (Merck and Co, Inc, Whitehouse Station, NJ, USA) prior to induction of sepsis via a cecal ligation and puncture model, lived 4 times as long as mice treated with placebo (Merx et al 2004). This survival benefit occurred despite similar rates of bacteremia. Pretreatment with simvastatin preserved cardiac contractility as measured 20 hours after ligation and puncture, compared with a 28% decline in cardiac output in control mice. Similarly, leukocytes isolated from treated mice displayed a reduced ability to adhere to cytokine-stimulated murine endothelial cells compared with leukocytes harvested from control mice. The same group of investigators has recently found similarly encouraging results when HMG-CoA reductase inhibitors are administered to mice after the onset of sepsis (Merx et al 2005). In an identical model, mice treated with statins lived twice as long as controls, despite not being treated until 6 hours after cecal ligation and puncture. Delaying treatment until after the manifestation of hemodynamic alterations did not prevent treated mice from again demonstrating preservation of cardiac function and decreased leukocyte–endothelial adherence.

Although no randomized, controlled studies have investigated the efficacy and safety of statins in treating humans with severe sepsis or septic shock, retrospective and

observational data suggest a possible benefit. A retrospective review of 388 cases of bacteremia from either aerobic gram-negative rods or *Staphylococcus aureus* demonstrated a reduction in both overall (6% vs 28%; $p=0.002$) and infectious mortality (3% vs 20%; $p=0.010$) in patients taking statins compared with those not taking statins (Liappis et al 2001). A recent prospective observational cohort study has found confirmatory data. This study evaluated 361 consecutive patients admitted to the hospital with presumed or documented acute bacterial pneumonia (Almog et al 2004). Severe sepsis, or organ dysfunction attributable to sepsis, developed in only 2.4% of patients who had been treated with statins for longer than a month prior to admission compared with 19% of patients not treated with statins ($p<0.0001$). Similarly, only 3.7% of patients treated with statins required care in the ICU compared with 12.2% of controls. Given these data, the relative risk of developing severe sepsis associated with statin use was calculated to be 0.13 (95% CI: 0.03–0.52) and the relative risk of requiring ICU care was 0.30 (95% CI: 0.1–0.95) (Almog et al 2004). Unfortunately, the observational nature of both of these studies yields significantly different baseline characteristics between groups. Not unexpectedly, patients receiving statins were more likely to be afflicted with hypertension, ischemic heart disease, diabetes, and hyperlipidemia. However, they also had significantly different sources of infection and were less likely to demonstrate hypoalbuminemia or poly-substance abuse (Liappis et al 2001; Almog et al 2004). These differences in baseline characteristics and uncontrolled administration of statins render cause and effect determinations impossible. Large, multicenter, randomized, blinded, placebo-controlled trials will need to be conducted to effectively answer the question of whether or not treating septic patients with statins improves clinical outcomes.

Conclusion

The complexity of medicine, including older patients with greater comorbidities, more immunosuppression, and an increasing use of invasive procedures, has resulted in a dramatic rise in the incidence of severe sepsis and septic shock. Despite the increasing burden on society, treatment options remain limited. Drotrecogin alfa (activated) has received regulatory approval for treatment of such patients, but investigations continue in an attempt to optimize its utilization. Replacement doses of corticosteroids and/or vasopressin may also help in select subpopulations of patients with septic shock.

The search for novel treatments has accelerated with the emerging comprehension of the complex pathophysiology. Animal data suggest that inhibiting late mediators of inflammation, such as HMGB1, or mediators of both inflammation and coagulation, like TF, may prove beneficial. Uncontrolled studies in humans also suggest that HMG-CoA reductase inhibitors, with their many pleiotropic actions, may both prevent and attenuate the septic state. Future investigations should continue to focus on improving clinical outcomes, especially mortality, and may benefit from a multifaceted approach of combining numerous agents with different actions.

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