Novel Therapies for Septic Shock Over the Past 4 Decades

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Infections that result in shock and organ failure are a major public health problem worldwide. Severe sepsis and septic shock affect patients of all ages and often complicate chronic diseases. They are the major causes of death in critical care units and contribute substantially to hospital inpatient costs. Translating the scientific advances of the last 4 decades into clinical practice has been challenging. Despite many attempts to develop new therapies, the basic elements of treatment have not changed since the 1960s. In this Grand Rounds, we summarize the results of the clinical trials conducted during the last 4 decades, discuss some lessons learned, and suggest possible directions for future investigation.

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CASE PRESENTATION

A young woman was admitted to the intensive care unit (ICU) with altered mental status, anuria, respiratory distress, and fever. She had undergone an allogeneic stem cell transplant 3 months previously for refractory large B-cell lymphoma but had recurrent disease requiring further chemotherapy. She was febrile, neutropenic, and was treated empirically with broad-spectrum antibiotics. During the 48 hours prior to ICU admission, she became anuric.

After arrival in the ICU, the patient developed respiratory distress requiring intubation and ventilatory support. Chest computed tomography scan revealed basilar consolidation and diffuse interstitial infiltrates. She required escalating doses of vasopressors to maintain blood pressure. Antibiotic coverage was broadened and stress doses of hydrocortisone were initiated. An echocardiogram revealed global hypokinesis of the left and right ventricles. Inotropes were added to the vasopressor infusions. Blood cultures obtained prior to ICU admission grew *Enterococcus faecium*. During the subsequent 24 hours, the patient required increasing vasopressor and inotrope support and continuous renal replacement therapy. Forty-eight hours after ICU admission she developed episodes of pulseless electrical activity, which culminated in refractory asystole.

The final clinical/anatomical diagnoses were refractory lymphoma, septic shock due to *E faecium,* cardiogenic shock secondary to chemotherapy-induced cardiomyopathy, and thrombotic microangiopathy causing acute renal failure.

This case illustrates many features of severe sepsis typically seen in referral centers today. The patient had an immunosuppressive primary disease treated with stem cell transplantation. The intensive chemotherapy worsened her immune deficiency and induced cardiomyopathy. The patient became bacteremic while neutropenic. Despite promptly receiving broad-spectrum antibiotics and supportive care, she developed microangiopathy, renal failure, and hemodynamic collapse that led to her death within a few days.

Major underlying disease, immunosuppression, bacteremia, antibiotic resistance, and refractory shock are common findings in patients who die from infectious diseases, but they are not universal. However, characteristics of patients with severe sepsis (infection-induced organ hypofunction) or septic shock (refractory hypotension) vary in many ways including age, underlying disease, microbial etiology, local infection site, and genetic makeup. Thus, devising new therapies for severe sepsis and septic shock has been difficult.[1]

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Improved therapies for septic shock are clearly needed. The incidence of sepsis has increased during the past 3 decades[2,3] as has its economic burden. Among the 10 conditions with the most rapidly increasing hospital inpatient costs from 2001-2007, septicemia demonstrated the largest growth in aggregate costs (174.1%) and the highest aggregate costs ($12.3 billion in 2007).[4] Significant improvements in patient outcomes may have resulted from more rapid diagnosis and treatment, yet the case-fatality rates for severe sepsis and septic shock remain high. Hospital mortality rates in international registries range from 30% to more than 50%.[5-7] Although remarkable scientific advances over 4 decades have provided new insights into the pathophysiology of severe sepsis and septic shock, translating these advances into clinical practice has been very difficult.[8] The basic elements of treatment have not changed since the 1960s: antibiotics; if present, prompt removal or drainage of an infected source (ie, source control); and cardiopulmonary resuscitation.[9]

Here, we review the classes of agents tested over the past 4 decades for their ability to successfully treat patients with severe sepsis and shock. We comment on how results of clinical trials have informed the understanding of the pathophysiology of septic shock and we propose potential future research directions.

Usual Therapy

The principles of removing a focus of infection and initiating broad-spectrum antibiosis antedated the current era by centuries and decades, respectively.[9,10] The cornerstones of therapy for sepsis and septic shock remain the prompt administration of empirical antibiotics that target the species and antibiotic sensitivities of the likely pathogens, the use of fluid resuscitation and vasopressors to reverse hypotension and maintain tissue perfusion,[11] and if possible, prompt removal or drainage of the source of the infection.

Therapies for Septicemia

The development of adjunctive therapies for sepsis has paralleled and often reinforced prevalent assumptions about the nature of sepsis. In the 1970s and 1980s, uncontrolled localized infection was thought to lead to bloodstream invasion by bacteria, their products (septicemia), or both, which subsequently induced harmful inflammation throughout the body. Attention focused on neutralizing gram-negative bacterial endotoxin, the best-studied trigger molecule, and antiendotoxin antibodies were tested in several trials. However, the strikingly positive results of the first human trial of antiendotoxin serum were never reproduced and 2 antiendotoxin monoclonal (IgM) antibodies also failed to show benefit.[12-14]

Similarly, a more specific endotoxin-neutralizing agent, recombinant bactericidal permeability–increasing protein, seemed to prevent morbidity (loss of limbs) when it was tested in children with fulminant meningococcemia, but survival did not improve.[15] These disappointing results diminished interest in endotoxin as a therapeutic target. Recently, 3 novel endotoxin antagonists were tested in clinical trials but failed to meet their primary end points and in some instances caused serious toxicities (online-only references 5-8 in the eTable available at http://www.jama.com).

Another approach to the immunotherapy of septicemia is the use of intravenous polyclonal immunoglobulin. A meta-analysis of 20 trials in adults with sepsis found the overall effects to be indeterminate because of methodological limitations and high levels of heterogeneity across the trials.[16]

Anti-inflammatory Therapies

The First Clinical Definitions. Definitions were devised in 1991 to facilitate comparisons and enrollment in clinical trials of new therapies for sepsis. They divided the clinical signs of infection into broad categories of increasing systemic severity[17]: (1) patients with fever, tachycardia, tachypnea, and altered white blood cell numbers had the systemic inflammatory response syndrome (SIRS); (2) if there was evidence of infection, they had sepsis; (3) if the infection was associated with decreased organ function (such as oliguria, hypoxemia, or delirium), patients were considered to have severe sepsis; and (4) those with persistent hypotension had septic shock. These stages represented a continuum of systemic inflammation with each stage having a greater associated risk of death.[17] Emerging from the idea that host inflammation is requisite in the development of shock and organ failure was the anticipation that anti-inflammatory interventions would improve outcomes.

High-dose glucocorticoids had been used for approximately 3 decades to reduce inflammation in patients with various infectious diseases. A meta-analysis of 9 trials conducted from 1963-1988 showed that short courses of high doses of steroids (median dose, 23 975 mg of hydrocortisone equivalents over a median of 1 day) actually worsened survival.[18] Following the discovery of tumor necrosis factor (TNF) and interleukin 1 (IL-1β), it was widely believed that these and other proinflammatory mediators produce the exuberant inflammatory response that leads to hypotension and organ injury. High-dose steroid therapy was abandoned in favor of testing agents that could selectively inhibit these proinflammatory molecules.

This approach has had limited success. A meta-regression analysis of 21 trials of agents that targeted single proinflammatory mediators showed that these agents (antagonists to TNF, IL-1 β, platelet-activating factor, bradykinin, and cyclooxygenase) had variable effects on survival.[19] Reconciling the dramatic success of these agents in preclinical evaluations with their failure to improve clinical outcomes in clinical trials was difficult. The authors of the meta-regression analysis noted that essentially all of the anti-inflammatory agents were tested in animal models of infection that had very high mortality rates. In contrast, the human trials were conducted in patients with a low or intermediate risk of dying. In prospective

animal studies, the same authors found that the survival benefit of different anti-inflammatory agents varied with illness severity.[19] Reviewing data from human trials in which patients could be stratified according to a severity of illness score, the authors noted a similar relationship—the agents generally improved survival in the sicker patients and were often harmful to the less sick. These observations suggest that anti-inflammatory drugs may only be useful for patients in whom the inflammatory response is very intense. Identifying these specific patients based on semiquantitative assessments of illness remains challenging.

A Reincarnation: Glucocorticoid Therapy for Severe Sepsis. In the late 1990s, interest emerged for using physiologic or stress doses of corticosteroids for patients with septic shock. Twelve small trials conducted after 1997 found that long courses of low doses of steroids (median dose, 1209 mg equivalents of hydrocortisone over a median of 6 days) were associated with improved survival. In a meta-analysis, a potential survival benefit was found in patients who at study entry were at high risk for dying.[18] Further, low-dose steroids have also been shown to decrease vasopressor requirements and enhance shock reversal.

A major limitation of the most recent studies of low doses of steroids in septic shock is that the beneficial effects were found primarily in small trials. In addition, the largest trial of low-dose steroids studied a low-risk population.[18,20] The beneficial effects of low-dose steroids have thus not been confirmed in a large, multicenter trial of high-risk patients. Until definitive data are available, the decision to administer low-dose steroids for septic shock should be based on an individual patient's severity of illness and potential risk from corticosteroid administration. The cosyntropin stimulation test has not been shown to be useful for this purpose.[18,21]

Anticoagulant Therapy. A new approach to treating septic patients was introduced in the late 1990s. Reasoning that thrombosis was a major contributor to organ injury during severe sepsis, 3 recombinant anticoagulant proteins were tested in clinical trials (online-only reference 17 in the eTable).[22,23] The trial of tissue factor pathway inhibitor was instructive; whereas the drug appeared to be lifesaving after 700 patients had been enrolled ($P=.006$), its efficacy decreased during the second phase of the trial and the overall outcome was negative.[22] An explanation for such dramatic inconsistency was not evident.

The apparent efficacy of drotrecogin alfa (activated) or human recombinant–activated protein C also changed as its pivotal trial proceeded.[23,24] By the end of the trial, 28-day mortality was lower in the activated protein C group; the absolute decrease in mortality was 6.1%. The trial was stopped early because of presumed benefit ($P=.005$) and activated protein C was approved by the US Food and Drug Administration for the treatment of severe sepsis in the highest-risk patients (APACHE II score >25).[24] However, when activated protein C was tested later in a low-risk population, the trial was stopped prematurely because of futility.[25] Interestingly, the patients in this trial who had an APACHE score greater than 25 and were treated with activated protein C did not experience the survival benefit observed in the first phase 3 trial.

Similarly, a pediatric trial was stopped because of futility.[26] The treatment effect has thus been inconsistent and activated protein C is now being reassessed in 2 new prospective trials.[27,28]

Although many authors have attributed activated protein C's apparent efficacy to its anti-inflammatory potency, it was tested in septic patients because of its anticoagulant properties. In the first 3 randomized trials, the rate of serious bleeding was approximately 1 patient in 20. In contrast, in a survey of postlicensure usage, the rate of serious bleeding was more than 3-fold higher than in the original trials.[29] Similarly, fatal events associated with the agent increased significantly and the risk of death was approximately 1 in 150.[30] Thus, while there was some enthusiasm for the use of activated protein C after its early approval, subsequent evidence has suggested that the risks of this agent may potentially outweigh its benefits.

Returning to Basics

In 2002, the Surviving Sepsis Campaign emerged to raise awareness of sepsis among the general public and health care professionals and to develop practice guidelines for the treatment of sepsis. The guidelines engendered controversy on 2 fronts; the role of pharmaceutical industry sponsorship and the grading of evidence used to support established and novel therapies for sepsis.[31,32] Aiming to standardize care and improve outcomes from sepsis, treatment guidelines for the Surviving Sepsis Campaign were incorporated into a performance improvement initiative. In an uncontrolled observational study, the authors of the guidelines noted a 5.4% decrease in mortality in participating centers over a 3-year period.[33] The true impact of this initiative remains uncertain because of methodological concerns and the lack of a control group.[34]

The Surviving Sepsis Campaign developed therapeutic bundles of resuscitation and management. In an analysis of 8 trials of outcome based on utilization of the components of the sepsis resuscitation and management bundles, bundle use was associated with an increase in survival.[35] However, the strongest association of bundle elements with improved outcomes was the decrease in time to antibiotic administration and antibiotic appropriateness. Assessing the importance of other components of the bundles on outcomes (eg, fluid administration, vasopressors, inotropes, erythrocyte transfusion titrated to hemodynamic goals, corticosteroids, and recombinant activated protein C) was limited by significant heterogeneity across the trials.[35] Three large international trials are currently investigating the validity and usefulness of the resuscitation bundle.[36-38] The importance of administering empirical antibiotics promptly has also been bolstered by new

evidence regarding the timing of antibiotic administration in relation to the clinical signs of septic shock. In a retrospective analysis,[39] every hour that antibiotics were delayed after the onset of hypotension was associated with an 8% increase in mortality.[39]

LESSONS LEARNED, FUTURE DIRECTIONS

Many phase 3 clinical trials have been conducted in patients with sepsis and septic shock. The tested agents included endotoxin antagonists[12-15] (references 5-9 in the eTable), intravenous immunoglobulins[16] (reference 11 in the eTable), high- and low-dose steroids[18,20] (reference 23 in the eTable), a nitric oxide synthase inhibitor (reference 1 in the eTable), inflammatory modulating agents[19] (references 12-16, 19-22 in the eTable), and anticoagulants[22,23,25,26] (references 17, 18 in the eTable). Initially positive results were not reproduced in subsequent trials.[40] Clinicians must be very cautious when interpreting the results of trials of new interventions in sepsis and critical illness. Reproducibility is vital to ensure that these adjuncts to clinical care are safe and efficacious.[40]

The trials of new therapies tested assumptions regarding the pathogenesis of severe sepsis. Most sought to improve outcome by removing a single proinflammatory factor from the mix. Others, notably glucocorticoids, would have provided broad immunosuppressive and vascular effects. The anticoagulants tested the role played of thrombosis in septic shock. It was also assumed in each instance that severe sepsis and septic shock have essentially identical pathogenetic mechanisms in patients who differ with respect to age, race, sex, premorbidities, illness severity, and infectious etiologies. Although standard of care supportive measures were also provided, as many as one-fourth of the patients in some trials received inappropriate antibiotics; in others, secondary infections were common. No trial required prompt antibiotic administration or considered the timing of antibiotic initiation in the efficacy analysis.

As noted in our clinical case, the ability of definitive antibiotic therapy and supportive care (ie, fluids, vasopressors, mechanical ventilation, and renal replacement therapy) to reverse the decline in organ function that leads to death may be limited by the burden of comorbid illness and compromised immunity. Effective new therapies are desperately needed.

We have also learned that patients who experience severe sepsis and septic shock are heterogenous in numerous ways, that very large clinical trials are needed to detect significant benefit or risk, that removing a single inflammatory mediator is unlikely to reverse the septic process, and that favorable results must be reproduced in more than 1 phase 3 trial prior to drug licensure. Perhaps the most useful lesson has been the recognition that immunomodulatory therapies should be directed to the most severely ill pa-

Table. Two Views of Sepsis Pathogenesis Using Gram-negative Bacteria as Examples

	Hypothesis[a]	
	Systemic Inflammation	Compartmentalization
General	Local and systemic defenses are a functional continuum Inflammatory responses within an infected extravascular tissue propagate throughout the body via the bloodstream	Local and systemic responses are compartmentalized Local tissue inflammation is accompanied and contained by systemic anti-inflammation (mediated by, eg, cortisol, epinephrine, IL-10, IL-1ra, and elements of the acute phase response) The central nervous system plays a major role in regulation
Role played by bacteremia	Uncontrolled infection results in bacteremia; when bacteria enter the bloodstream, they trigger toxic reactions	If bacteria enter the blood, their ability to stimulate toxic responses is limited by systemic anti-inflammation and numerous mechanisms that neutralize bacterial endotoxin Harmful systemic responses are mainly induced by uncontrolled infection and inflammation in tissues, not the bloodstream
Basis for organ hypofunction, shock	Intravascular responses to circulating bacteria and/or proinflammatory mediators precipitate organ failure and shock Microthrombosis, endothelial cell injury, leukocyte- or complement-mediated damage are prominent	Organ hypofunction and shock are maladaptive consequences of conserved responses that are initially adaptive (eg, mechanisms that promote energy conservation early during the host response may impair cellular function as they intensify, continue for long periods of time, or both)
Recovery mechanisms	Counter-regulatory (anti-inflammatory) molecules restore balance and allow return to homeostasis The anti-inflammatory response may also be immunosuppressive	Immunosuppression results in part from systemic anti-inflammation Recovery is regulated by both local resolution/repair mechanisms and the nervous system
Prototype agents	*Neisseria meningitidis, Yersinia pestis, Burkholderia pseudomallei, Vibrio vulnificus*	*Escherichia coli, Enterobacter*, and *Klebsiella* species
Experimental models	Intravenous infusion of endotoxin or bacteria, infection models that rapidly result in high levels of bacteria	Infection models that produce local infection/inflammation with or without delayed bacteremia

Abbreviation: IL, interleukin.
[a] Hypotheses represent extremes; many host-pathogen encounters have elements of both. Data adapted from Munford,[41] 2006.

tients in whom the benefit gained by suppressing local inflammation may exceed the risk that host defense will be impaired.

Many clinicians have also begun to question the dogma that severe sepsis and septic shock are caused by systemic inflammation.[41] Two possible alternative views are shown in the TABLE. Indeed, the SIRS concept has been undermined by numerous observations that early systemic responses to infection actually prevent inflammation in the bloodstream and that patients with severe sepsis are usually profoundly immunosuppressed.[42,43] An evolution-based explanation for organ hypofunction and shock is gaining ground, stating that beneficial (adaptive) early systemic reactions to infection may become maladaptive when they are driven by uncontrolled local infection or inflammation.[44]

Several widely used terms may have been limiting. It is important now to find terms that avoid dichotomous and poorly defined categories (proinflammatory vs anti-inflammatory, local vs systemic) and colorful but uninformative labels (cytokine storm and organ failure).[45] Does a patient who has fever and tachycardia while also having influenza really have sepsis? The procrustean SIRS definitions, intended to simplify and standardize clinical thinking, may have discouraged other views.

It is also imperative to acknowledge the complexity, nonlinearity, and integration of the body's responses to infection and other stresses. These components of the host response to infection, which have only recently begun to be studied, are providing a broadened view of host-pathogen interaction.[46]

We have also learned that most deaths do not occur during the first week following the onset of severe sepsis or shock, the time when each of the immunomodulatory and anticoagulant drugs was given. Instead, loss of life continues throughout and beyond the 28-day observation period used for the clinical trials.[47,48] Attributable deaths have been noted as long as 5 years later, as has significant loss of cognitive ability and functional impairment.[49] Drugs intended to rescue patients from the acute crisis of severe sepsis or shock may have little effect on events that occur weeks or months later.

By focusing on salvage therapies for the sickest patients, we may have overlooked the fact that more than 90% of previously healthy young patients survive severe sepsis.[50] With appropriate antibiotics and supportive care, the body's recovery mechanisms work well. Sepsis-induced organ hypofunction is usually reversible. Understanding how the previously healthy, young human body responds to infection could uncover important clues about how harmful responses develop in older individuals and in those with significant comorbidities.

Little is known about how the body's normal recovery mechanisms are altered by severe sepsis. Emphasis has been placed on immunosuppression, which seems to be a predictable consequence of severe stress, but how other phenomena contribute to delayed resolution of organ hypofunction is unknown.[43] Understanding how immunosuppression is induced and maintained in patients with severe sepsis should be a major goal for sepsis research.

Finally, rapidly giving appropriate antimicrobial chemotherapy almost certainly saves lives. Analytical plans for future studies of adjunctive therapies should include a previously ignored variable—the time interval from onset of signs of infection or severe sepsis to the initiation of appropriate antibiotics.

The future should bring a new emphasis on understanding both sepsis pathophysiology and the body's normal recovery mechanisms. We anticipate that new biomarkers will be found and used to target drugs to patients' specific needs. We can look forward to new approaches that will restore immunocompetence and enhance recovery in patients who survive the acute crisis of severe sepsis or septic shock. We are confident that rapid, appropriate antibiotic therapy and source control will remain the foundation on which adjunctive interventions will be built.

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