Sepsis: A Clinical Update

Corey E. Ventetuolo and Mitchell M. Levy

Department of Medicine, Brown University, Providence, Rhode Island


The burden of sepsis on our health care system is significant, with approximately 750,000 cases per year in the United States, 215,000 resultant deaths, and annual costs of $16.7 billion nationally (1). Organ failure is a significant contributor to mortality, with renal failure occurring in approximately 15% of patients (2). In a large registry of critically ill patients with acute renal failure, in 19% of whom was sepsis identified as the presumed cause, in-hospital mortality was 37% with a combined outcome of death or dialysis dependence in 50% (3). Clinicians are challenged to manage this disease in an aging population with multiple comorbidities, immunosuppression, and a changing pattern of causative microorganisms (2,4).

The increasing incidence of sepsis and the unacceptably high mortality rates associated with the disease have led to global efforts to understand pathophysiology, improve early diagnosis, and standardize management (5). Understanding the spectrum of the disease is important for gauging severity, determining prognosis, and developing methods for standardization of care in sepsis. At an international consensus conference in 1991, sepsis was defined as the systemic inflammatory response syndrome (SIRS) with a suspected source of infection. SIRS is defined as two or more of the following perturbations: Temperature >38 or <36°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or Paco₂ <32 mmHg; and white blood cell count >12,000/mm³, <4000/mm³, or >10% immature band forms. Organ dysfunction and hypoperfusion abnormalities characterize severe sepsis, and septic shock includes sepsis-induced hypotension despite adequate fluid resuscitation (6). These definitions allowed for a more uniform approach to clinical trials, hypothesis generation, and the care of the patient with sepsis.

The use of SIRS criteria for the identification of sepsis have been believed by many to be arbitrary and nonspecific. In 2001, the terminology was revisited in another consensus conference. At that time, the primary categories of sepsis, severe sepsis, and septic shock were confirmed as the best descriptors for the disease process. The primary change introduced was a more comprehensive list of signs and symptoms that may accompany the disease. In addition, a staging system was proposed for the purpose of incorporating both host factors and response to a particular infectious insult. This concept, termed PIRO (predisposition, infection, response, organ dysfunction) (7) speaks to the need to define, diagnose, and treat patients with sepsis more precisely because a variety of evidence-based interventions now exist to improve outcomes (8–10) in severe sepsis and septic shock. The PIRO model remains hypothetical and is being evaluated in several studies.

Pathophysiology: Mediators of Sepsis

Integral to the development of diagnostic and management strategies is an understanding of the interplay among the host’s immune, inflammatory, and procoagulant responses in sepsis. When a given infectious agent invades the host, an innate response is triggered via toll-like receptors (TLR). TLR are transmembrane proteins with the ability to promote signaling pathways downstream (11), triggering cytokine release and neutrophil activation and stimulating endothelial cells. Activation of humoral and cell-mediated immunity follows with specific B and T cell responses and both pro- and anti-inflammatory cytokine release (12). Proinflammatory mediators, including TNF-α, IL-1β, and IL-6, and anti-inflammatory mediators, including IL-10, IL-1 receptor antagonists, and soluble TNF receptors, both are significantly upregulated in patients with severe sepsis (13).

As adaptive immunity is triggered and the inflammatory cascade of sepsis unfolds, the balance is shifted toward cell death and a state of relative immunosuppression. At this late stage, accelerated lymphocyte apoptosis occurs (14), and proinflammatory mediators, including TNF-α, IL-1β, and IL-6, may be downregulated (15). Innate defects in neutrophil response and host immunity may also play a role (16). End-organ dysfunction ensues. Various mediators, including TNF-α and IL-1β (17), induce nitric oxide (18) and cause myocardial depression and left ventricular dilation with decreased ejection fraction and systemic vascular resistance. The end result of these hemodynamic changes is an elevated cardiac output and generalized vasodilation. This is often described as “high-output” shock. As the inflammatory response progresses, myocardial depression becomes more pronounced and may result in a falling cardiac output. Altered Starling forces from vasodilation and endothelial dysfunction prompted by mediator release lead to capillary leak and pulmonary edema that may progress to acute lung

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Mitchell M. Levy, Rhode Island Hospital/Brown University, 593 Eddy Street, Providence, RI 02903. Phone: 401-444-2776; Fax: 401-444-3002; E-mail: Mitchell_levy@brown.edu.
injury and acute respiratory distress syndrome (ARDS). A surge in catecholamines, angiotensin II, and endothelin causes renal vasoconstriction and increases risk for nephrotoxicity with renal failure (19). These changes are accompanied by alterations in the coagulation cascade toward a procoagulant and antifibrinolytic state. Increased thrombin, via tissue factor upregulation, leads to endothelial and platelet activation as well as vascular smooth muscle changes. As a result, there is fibrin deposition and microvascular thrombosis, which may threaten end organs. The development of disseminated intravascular coagulation in severe sepsis is a predictor of death and the development of multiorgan failure (20). Antithrombin III, protein C, protein S, and tissue factor pathway inhibitor levels are decreased in severe sepsis, leading to a prothrombotic, antifibrinolytic state (20,21). Formation of activated protein C (APC) is also impaired (22). In the normal state, APC acts as an important anticoagulant (23) and inhibits fibrinolysis via plasminogen activator inhibitor inactivation (24). In addition, APC has been shown to reduce proinflammatory cytokine release and inhibit leukocyte adhesion (25) and endothelial cell apoptosis (25,26).

Diagnostic Challenges in Sepsis

Despite advances in our understanding of the disease’s mechanisms, it remains difficult to apply these lessons clinically toward early diagnosis and treatment. Addressing this dilemma is paramount given the availability of life-saving interventions (8), interventions that lose their mortality benefit when delivered late (27,28). As the host’s initial compensatory mechanisms are overwhelmed and a patient moves through the disease spectrum, tissue beds become hypoxic and injury occurs at the microvascular level. The resultant tissue hypoperfusion, which characterizes severe sepsis and septic shock, can occur despite normal clinical parameters, including vital signs and urine output, and may continue after initial resuscitation (8,29). Failure to intervene at this stage, before or early in the development of organ dysfunction, results in increased morbidity and mortality (30). Poor outcomes in severe sepsis have been correlated to the development of organ failure on as early as day 1 of presentation (31).

In addition to developing a more comprehensive definition and staging system for identifying patients early, lactate and central venous (superior vena cava; ScvO$_2$) or mixed venous oxygen saturation (SvO$_2$) have been used as surrogate markers to identify patients with an imbalance of oxygen supply and demand, who are, therefore, at risk. Although lactate itself lacks precision, in the appropriate clinical setting, an elevated level ($\geq$4 mmol/L) is indicative of tissue hypoperfusion and an independent predictor of mortality (32,33). In the initial inflammatory phase, there is often an increase in oxygen delivery, which may be associated with a fall in ScvO$_2$ or SvO$_2$ as a result of an inadequate cardiovascular response. As the inflammatory response progresses, there are regional alterations in the microcirculation, leading to an elevation in ScvO$_2$ or SvO$_2$ (34).

Knowledge of the relationships between these surrogates and efforts to optimize oxygen supply and demand in patients with severe sepsis evolved into goal-directed therapy. Rivers et al. (8) found a significant reduction in 28-d mortality when applied early (within 6 h of emergency department presentation) versus standard therapy (30.5 versus 46.5%; $P = 0.009$). Early goal-directed therapy (EGDT) refers to a protocol that targets a normal central venous pressure and ScvO$_2$ or SvO$_2$ in these critical early hours of sepsis. When intravenous fluids fail to achieve these targets, red blood cells are transfused and inotropic support with dobutamine is added to augment oxygen delivery. Although there was no direct assessment of the impact of EGDT on renal outcomes, various physiologic scoring systems (Acute Physiology and Chronic Health Evaluation II [APACHE II], Simplified Acute Physiologic Score II, and Multiple Organ Dysfunction Score) were assessed serially between 7 and 72 h and were significantly improved ($P < 0.001$) in the EGDT group. As discussed next, EGDT is considered a critical intervention in the early treatment of patients with severe sepsis.

Management of Severe Sepsis: A New Standard of Care

The publication of several randomized, controlled trials demonstrating mortality reduction with certain interventions in severe sepsis (8–10), along with the desire to integrate evidence-based medicine into clinical practice, led to the development of the Surviving Sepsis Campaign guidelines (5). In partnership with the Institute for Healthcare Improvement, the Surviving Sepsis Campaign designed the resuscitation and management bundles in an effort to facilitate knowledge transfer and establish best-practice guidelines. They are to be completed within the first 6 and 24 h, respectively, of a patient’s care (Table 1). Evidence supporting each element of the bundles is beyond the scope of this review, but some key discussion points follow.

Appropriate Antibiotics

Broad-spectrum intravenous antibiotics should be administered promptly after appropriate cultures are obtained. Although it is widely recognized that failure to initiate adequate antimicrobial coverage results in adverse outcomes (35,36), recent epidemiologic studies have shown a significant increase in the frequency of severe sepsis from polymicrobial infection (4). Multidrug-resistant bacteria, such as *Pseudomonas* species and methicillin-resistant *Staphylococcus aureus*, as well as other Gram-positive and fungal organisms, are also increasing (2). Knowledge of these changing microbiologic patterns, as well as host and local patterns of susceptibility, are critical in selecting initial therapy. Institution of timely antimicrobial therapy is equally important in the care of the patient with sepsis. A recent retrospective review of 2731 cases of septic shock demonstrated a strong relationship between delay in appropriate antibiotics and in-hospital mortality; administration of antibiotics beyond the first hour of presentation resulted in decreased survival with each additional hour that therapy was delayed (37).

EGDT

After the original publication detailing EGDT (8), controversy has surrounded some aspects of the protocol. An in-
Table 1. Surviving Sepsis Campaigna

<table>
<thead>
<tr>
<th>Sepsis Resuscitation Bundle</th>
<th>Sepsis Management Bundle</th>
</tr>
</thead>
<tbody>
<tr>
<td>The goal is to perform all indicated tasks 100% of the time within the first 6 h of identification of severe sepsis.</td>
<td>Efforts to accomplish these goals should begin immediately, but these items may be completed within 24 h of presentation for patients with severe sepsis or septic shock.</td>
</tr>
<tr>
<td>measure serum lactate</td>
<td>administer low-dosage steroids for septic shock in accordance with a standardized ICU policy; if not administered, then document why the patient did not qualify for low-dosage steroids based on the standardized protocol</td>
</tr>
<tr>
<td>obtain blood cultures before antibiotic administration</td>
<td>administer rhAPC-Xigris in accordance with a standardized ICU policy; if not administered, then document why the patient did not qualify for rhAPC</td>
</tr>
<tr>
<td>administer broad-spectrum antibiotic within 3 h of ED admission and within 1 h of identification of sepsis on the hospital floor</td>
<td>maintain glucose control ≥70 but &lt;150 mg/dl</td>
</tr>
<tr>
<td>in the event of hypotension and/or a serum lactate &gt;4 mmol/L</td>
<td>maintain a median IPP 30 cmH2O for mechanically ventilated patients</td>
</tr>
<tr>
<td>deliver an initial minimum of 20 ml/kg crystalloid or equivalent</td>
<td></td>
</tr>
<tr>
<td>apply vasopressors for hypotension not responding to initial fluid resuscitate</td>
<td></td>
</tr>
<tr>
<td>to maintain MAP &gt;65 mmHg</td>
<td></td>
</tr>
<tr>
<td>in the event of persistent hypotension despite adequate fluid resuscitation (septic shock)</td>
<td></td>
</tr>
<tr>
<td>and/or lactate &gt;4 mmol/L</td>
<td></td>
</tr>
<tr>
<td>achieve a CVP ≥8 mmHg</td>
<td></td>
</tr>
<tr>
<td>achieve an ScvO2 ≥70% or SvO2 ≥65%</td>
<td></td>
</tr>
</tbody>
</table>

*CVP, central venous pressure; ED, emergency department; ICU, intensive care unit; IPP, inspiratory plateau pressure; MAP, mean arterial pressure; rhAPC, recombinant human activated protein C; ScvO2, central venous oxygen saturation; SvO2, mixed venous oxygen saturation

Vasopressin

For patients who have been fluid resuscitated, have achieved optimal central venous pressure, and continue to have vasopressor refractory shock, consideration can be given to adding low-dosage, time-limited vasopressin. Unlike traditional catecholamines, vasopressin causes direct vasoconstriction, through a variety of mechanisms (19). Its effects are organ system specific, however, with vasoconstriction occurring in the splanchnic beds and vasodilation occurring in the pulmonary and coronary circulation. GFR is increased via efferent arteriole constriction and increased filtration pressure. In early sepsis, there is an excess of endogenous vasopressin. Ultimately, levels return to normal range, creating a state of relative vasopressin insufficiency in the patient with severe septic shock (41). When appropriate, the addition of vasopressin allows for a reduction in standard vasopressors and may improve urine output and creatinine clearance (42). It should be used with caution in patients who are at risk for cardiac ischemia and low cardiac output. The dosage in clinical practice is 0.01 to 0.04 U/min, with a usual dosage of 0.03 U/min. There is no advantage to dosage titration beyond 0.04 U/min, and some studies have suggested a deleterious impact on organ perfusion at higher dosages.

Corticosteroids

There is controversy surrounding the use of corticosteroids in severe sepsis. The appropriate dosage and timing of therapy, as...
well as how best to evaluate the adrenal axis, has been studied and debated. High-dosage corticosteroids (>300 mg/d hydrocortisone) are not recommended and may cause harm (43). There has been a renewed interest in corticosteroids as we have come to understand sepsis as a state of relative adrenal insufficiency, albeit a state that is difficult to diagnose and define on the basis of various measurements of cortisol secretion (44).

A single, multicenter, randomized, controlled trial in which patients with refractory shock despite vasopressors and volume resuscitation received either hydrocortisone (50 mg intravenously every 6 h) and fludrocortisone (50 μg/d) or placebo for 7 d showed a mortality benefit at 28 d (53 versus 63% respectively; \( P = 0.02 \)) (9). In addition, vasopressors were withdrawn more frequently in the treatment group (57 versus 40%; \( P = 0.001 \)). This benefit was seen only in patients who did not respond appropriately to adrenocorticotropic hormone stimulation, with 229 of 299 patients classified as nonresponders (defined as a cortisol increase <9 μg/dl). A recent meta-analysis that included 16 trials and 2063 patients confirmed similar results and, importantly, noted no increase in the rate of adverse effects from corticosteroids (45); therefore, it is recommended that the use of low-dosage corticosteroids (hydrocortisone 200 to 300 mg/d in divided doses for 7 d) be considered in hypotensive patients with vasopressor-dependent septic shock. If a corticotropin stimulation test is obtained, then the clinician may elect to discontinue steroids in patients who respond appropriately.

**APC**

Therapeutic attempts to target the procoagulant nature of sepsis have been disappointing (46,47), with the exception of drotrecogin α (activated) or recombinant human APC (rhAPC). This may be due in part to alternative mechanisms of action. Recalling the pathophysiology of severe sepsis, rhAPC has antiapoptotic and anti-inflammatory activity and modulates endothelial dysfunction (25,26).

rhAPC is approved for the treatment of severe sepsis in patients with a high risk for death (defined as an APACHE II score >25), sepsis-induced multiple organ failure, septic shock, or sepsis-induced ARDS. In a multicenter, randomized, controlled trial of 1690 patients, treatment with drotrecogin α (activated) was associated with a 19.4% relative reduction and a 6.1% absolute reduction in the risk for death (\( P = 0.005 \)) (10). Although renal outcomes were not specifically examined, subgroup analysis, including APACHE II scores and number of dysfunctional organs or systems, demonstrated a persistent treatment effect. This mortality benefit was not seen in patients with a low risk for death (i.e., APACHE II score <25 or single-organ failure) and resulted in the termination of the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trial at interim analysis (48).

The risk for bleeding must be considered, and the drug is contraindicated in certain settings. The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial (10) excluded patients with platelet counts <30,000/mm³, surgery within the past 12 h, stroke within 3 mo, uncorrected gastrointestinal bleeding within 6 wk, and trauma. Patients who had ESRD and were on HD were also excluded. A higher incidence of serious bleeding events in the treatment group (3.5 versus 2.0%; \( P = 0.06 \)) occurred in PROWESS and was confirmed in a follow-up study (49).

Although considerable controversy exists, current consensus guidelines recommend rhAPC (5). In the appropriate clinical setting, rhAPC should be considered in the treatment of severe sepsis. It is recommended that hospitals develop a standardized policy to guide the use of rhAPC. Bedside assessment should inform decisions about risk assessment. Once a patient is determined to be at high risk for death, infusion of rhAPC should begin. Benefits of treatment are seen irrespective of pathogen or site of infection (50), and the drug is cost-effective (51) when used appropriately.

**Glucose Control**

Critical illness is often characterized by hyperglycemia and insulin resistance. Hyperglycemia may have detrimental effects at the cellular level and contribute to organ failure and morbidity and ultimately death. In a landmark randomized, controlled trial that investigated intensive (blood glucose level 80 to 110 mg/dl) versus conventional (blood glucose 180 to 200 mg/dl) insulin therapy in a surgical intensive care unit (ICU), intensive therapy resulted in a significant reduction in ICU and in-hospital mortality (52). This benefit was most pronounced in patients with a demonstrable septic focus and multiorgan failure, although the study involved primarily cardiac surgery patients. Several markers of morbidity were also significantly improved. Renal injury, defined as peak plasma creatinine >2.5 mg/dl, peak plasma urea nitrogen >54 mg/dl, or the need for renal replacement therapy, was significantly reduced in the intensive insulin group. *Post hoc* analysis demonstrated a more modest but persistent treatment effect with the maintenance of blood glucose levels <150 mg/dl, and, in the interest of avoiding hypoglycemia, current recommendations suggest this as a target (5,53). It seems that mortality benefit is derived from normoglycemia rather than insulin replacement itself, whereas in the prevention of renal injury, insulin dosing seems to play a role (53).

More recently, Van den Berghe et al. (54) examined intensive insulin therapy in the medical ICU population. Using the same targets for blood glucose control, intensive insulin therapy failed to provide a mortality benefit. Renal injury was significantly reduced (8.9 to 5.9%; \( P = 0.04 \)) as was duration of mechanical ventilation. There was an increase in mortality among patients in the intensive insulin group who stayed <3 d in the ICU. When ICU length of stay exceeded 3 d, rate of death was decreased. The authors speculated that this disparity may have resulted from earlier withdrawal of care among those with short lengths of stay (suggested on *post hoc* analysis) or that the effects of intensive therapy may take more time to be realized (54). Although more data are needed on the medical population to establish ideal targets for blood glucose, moderate control (blood glucose <150 mg/dl) is reasonable and likely to provide morbidity and, in patients with extended ICU stays, mortality benefit.
Mechanical Ventilation
Acute lung injury (ALI) or ARDS complicating severe sepsis or septic shock should be managed with a goal to avoid large tidal volumes and elevated plateau pressures. The largest trial that examined a volume- and pressure-limited ventilation strategy, by the ARDS Clinical Trials Network, demonstrated a significant mortality benefit in the group treated with a low tidal volume strategy (tidal volume of 6 ml/kg predicted body weight and plateau pressure <30 cmH2O) as compared with a traditional ventilation strategy (12 ml/kg predicted body weight and plateau pressure <50 cmH2O; 31.0 versus 39.8%, respectively; P = 0.007) (55). In addition, the group that was treated with lower tidal volumes experienced less organ, including renal, failure. In an animal model of ARDS, those that were subjected to higher tidal volumes had higher rates of epithelial cell apoptosis in the kidney and small intestine, as well as elevated levels of biomarkers correlated with renal injury (56). This strategy may occur at the expense of a normal pH and partial pressure of arterial carbon dioxide (so-called “permissive hypercapnea”)—abnormalities that may be tolerated when modest or offset with sodium bicarbonate infusion when severe.

Considerations for the Nephrologist
The development of acute renal failure is common in severe sepsis and has a significant impact on morbidity, mortality, and cost (1,19). Administration of bicarbonate does not improve hemodynamic instability, lactic acidosis, or response to vasopressors (57,58), and the use of low-dosage dopamine does not provide sustainable renal protection or improve outcomes in critically ill patients (59,60). Although the use of erythropoietin has not been studied specifically in severe sepsis, it has been shown to reduce transfusion requirements in critical illness but has no effect on outcome (61,62). It is therefore not recommended for patients with sepsis.

There is evidence for equivalence of continuous and intermittent renal replacement therapies for critically ill patients, although hemodynamic considerations are likely to dictate mode of therapy (63,64). Although preliminary data suggested that deleterious inflammatory mediators could be removed with the use of continuous hemofiltration (65), a randomized, controlled trial that examined the use of early continuous hemofiltration before the development of renal failure failed to show a reduction in circulating mediators or prevention of organ dysfunction (66).

Future Directions
The future management of sepsis will most likely involve therapies directed at newer inflammatory targets. Several such molecules are under investigation and include, among others, TLR4; the receptor for advance glycation end products; and high mobility group box 1 (HMGB1), a cytokine-like molecule that promotes TNF release from mononuclear cells. HMGB1 is actively secreted by immunostimulated macrophages and enterocytes and is also released by necrotic but not apoptotic cells. HMGB1 is now recognized as a proinflammatory cytokine (67).

The use of biomarkers to diagnose, stage, and assess risk is an important new field of study. Pro-calcitonin, C-reactive protein, IL-6, and other mediators may be used in combination to develop an “ECG” of sepsis that may ultimately help guide clinicians to early diagnosis and assist in determining appropriate treatment strategies (68).

Another important area of ongoing and future research is endothelial cells and the microcirculation. Better insight into endothelial cell and microcirculatory dysfunction may direct interventions that will facilitate enhanced restoration of tissue perfusion, a primary pathophysiologic lesion in the inflammatory process that contributes to multiorgan failure and cellular dysfunction in sepsis.

Conclusions
Severe sepsis and septic shock are common and increasing among the critically ill. The opportunity now exists for clinicians to adopt an evidence-based approach to diagnosis and management. Mortality may be reduced by focusing on early diagnosis, targeted management, and standardization of the care process.

Disclosures
Grant Support: Novartis, ESAI, Brahms. Speaker’s bureau: Eli Lilly, Brahms.

References


25. Joyce DE, Gelbert L, Ciaccia A, DeHoff B, Grinnell BW: Gene expression profile of antithrombotic protein C de-