

# Advances in the Management of Sepsis and the Understanding of Key Immunologic Defects

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## ABSTRACT

Anesthesiologists are increasingly confronting the difficult problem of caring for patients with sepsis in the operating room and in the intensive care unit. Sepsis occurs in more than 750,000 patients in the United States annually and is responsible for more than 210,000 deaths. Approximately 40% of all intensive care unit patients have sepsis on admission to the intensive care unit or experience sepsis during their stay in the intensive care unit. There have been significant advances in the understanding of the pathophysiology of the disorder and its treatment. Although deaths attributable to sepsis remain stubbornly high, new treatment algorithms have led to a reduction in overall mortality. Thus, it is important for anesthesiologists and critical care practitioners to be aware of these new therapeutic regimens. The goal of this review is to include practical points on important advances in the treatment of sepsis and provide a vision of future immunotherapeutic approaches.

**S**EPSIS is defined as the systemic inflammatory response that occurs during severe infection.<sup>1–4</sup> Severe sepsis is the syndrome of sepsis that is complicated by the development of organ failure.<sup>5–7</sup> Patients with sepsis often present in dramatic fashion with high spiking fevers, shock, and respiratory failure.<sup>2–7</sup> Due in part to this striking presentation, the

prevailing theory of sepsis for many years had been that sepsis represented an uncontrolled inflammatory response.<sup>5,6</sup> Lewis Thomas popularized this concept when he hypothesized that it was the host response, rather than the microorganisms, most responsible for the morbidity and mortality associated with the disorder. He conjectured: “the microorganisms that seem to have it in for us turn out to be more like bystanders .... It is our response to their presence that makes the disease. Our arsenals for fighting off bacteria are so powerful ... that we are more in danger from them than the invaders.”<sup>8</sup> The discovery of a number of potent cytokines, including tumor necrosis factor (TNF) and interleukin-1 (IL-1), which are increased in patients with sepsis and which when injected into animals reproduced many of the clinical and laboratory features of sepsis, supported this theory and led to the concept of sepsis as a “cytokine storm.”<sup>5–7</sup> In selected instances of sepsis (for example, meningococcemia), circulating TNF- $\alpha$  concentrations are increased markedly and correlate with survival. Based on this theory that the host “cytokine storm” response causes uncontrolled hyperinflammation and organ injury, pharmaceutical companies initiated numerous clinical trials (*e.g.*, TNF and IL-1 antagonists) in sepsis.<sup>9–13</sup> The results of more than 25 trials of various antiinflammatory agents showed no benefit or, in some cases, worsened survival. These dismal results caused some investigators to call for a reevaluation of our fundamental understanding of the pathophysiology of sepsis.<sup>5,6,14</sup>

As investigators took a new look at previous studies of the host response in sepsis and as additional studies were performed, evidence mounted that a proinflammatory and an opposing antiinflammatory response occurred concurrently in patients with sepsis.<sup>5,15</sup> Studies of circulating cytokines in patients with sepsis showed that in addition to proinflammatory cytokines, the potent antiinflammatory cytokine IL-10 was present in excess. Van Dissel *et al.* examined cytokine profiles and mortality in 464 patients admitted to the hospital with presumed infections and reported that a high ratio of IL-10 to TNF- $\alpha$  was associated with a fatal outcome in patients with community-acquired infection.<sup>16</sup> Other investigators reported that sepsis induced defects in the production of both pro- and antiinflammatory cytokines (*i.e.*, a global depression in all cell cytokine production).<sup>17–20</sup> Ertel *et al.*

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stimulated whole blood from septic and nonseptic critically ill patients with lipopolysaccharide and reported that production of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in septic patients' blood was frequently less than 10–20% that of control nonseptic patients.<sup>17</sup> Similarly, Sinistro *et al.* stimulated peripheral blood monocytes from septic or control patients and quantitated the percentage of cells producing proinflammatory cytokines.<sup>20</sup> Less than 5% of monocytes from septic patients produced cytokines, a value less than one third the percentage of cytokine-producing cells of controls.<sup>20</sup> Weighardt *et al.* studied lipopolysaccharide-stimulated production of cytokines by monocytes in patients with sepsis after abdominal surgery.<sup>21</sup> Postoperative sepsis was associated with an immediate defect in monocyte production of pro- and antiinflammatory cytokines. Patient survival was associated with recovery of the inflammatory but not antiinflammatory response. Collectively, these blood studies indicate that pro- and antiinflammatory cytokines can be produced rapidly after sepsis onset and that sepsis does not always induce unbridled hyperinflammation.

The seminal discovery of cell signaling receptor pathways involving pathogen recognition led to further advances in our understanding of sepsis but also yielded surprising results. Cells of the innate immune system recognize pathogens and initiate responses *via* pattern-recognition receptors termed Toll-like receptors (TLRs).<sup>22–24</sup> TLRs are a family of cell pattern recognition receptors that recognize molecules that are widely shared by various pathogens, including Gram-positive and Gram-negative bacteria, fungi, and viruses.<sup>22,23</sup> After TLR activation by the pathogenic antigens, adapter proteins are recruited, and there is subsequent rapid activation of numerous protein kinases.<sup>23</sup> Ultimately, cell signaling leads to induction of genes involved in the regulation of inflammation with increased production of pro- and antiinflammatory cytokines. Investigators initially assumed that blocking these receptors might ameliorate the symptoms of sepsis, and studies in mice with genetic deletion of TLRs did show that these mice are highly resistant to lethal endotoxin.<sup>23,24</sup> However, studies in TLR knockout mice and studies in which the TLR pathway was pharmacologically inhibited demonstrated *higher* mortality in TLR-deficient mice than in control mice when more clinically relevant authentic bacterial models of sepsis were used.<sup>25,26</sup> These studies, which demonstrate that blocking TLRs can have detrimental effects in sepsis, are analogous to studies showing that blocking TNF, a key proinflammatory cytokine that is released after TLR activation of macrophages, worsens survival in animal models of sepsis.<sup>27,28</sup> For example, Moore *et al.* reported that blocking TNF- $\alpha$  in murine sepsis caused by *Klebsiella pneumoniae* resulted in decreased bacterial clearance and worsened survival.<sup>28</sup> Rijneveld *et al.* observed that blocking TNF enhanced bacterial outgrowth and increased mortality in a murine pneumococcal pneumonia model of

sepsis.<sup>27</sup> In a related manner, studies show that TNF and IL-1 antagonists that are used in the treatment of patients with autoimmune diseases (*e.g.*, etanercept in patients with rheumatoid arthritis) actually increase the risk of sepsis. The recent failure of the TLR 4 antagonist eritoran in a phase 3 clinical trial in sepsis underscores the difficulty in treating sepsis by blocking the ability of cells to recognize and respond to pathogens.¶ The “take home” message from these various TLR antagonism studies seems to be that one must approach cautiously the idea of blocking the ability of the host to sense and respond to invading pathogens. Teleologically, these receptors exist to serve as an early warning of infection and help mount an expeditious response. It is possible that in selected individuals, downmodulation of this pathway may be advisable, but it must be done in a graded fashion and perhaps only after the initial immune response has been activated.

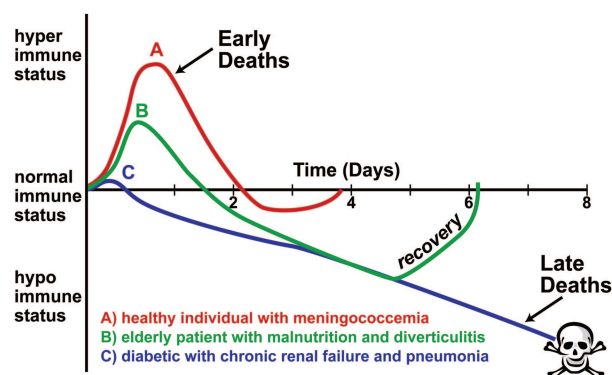
### Current Understanding of the Host Immunologic Response in Sepsis

Although there is still considerable debate, a growing consensus is that sepsis initiates pro- and antiinflammatory responses, both of which begin rapidly after life-threatening infection.<sup>14,29–31</sup> Although pro- and antiinflammatory processes begin promptly after sepsis onset, in general there is predominance of an initial hyperinflammatory phase, the magnitude of which is determined by a number of factors, including pathogen virulence, bacterial load, host genetic factors, and host comorbidities (fig. 1). For example, a previously healthy young adult who experiences meningococemia likely will exhibit a profound hyperinflammatory cytokine-storm-mediated response manifested by cardiovascular collapse, high fever, and multiorgan failure. If death occurs in the first few days of the illness, it most likely will be attributable to this uncontrolled cytokine-mediated response. In contrast, an elderly patient with diabetes who has required long-term hemodialysis and who experiences pneumonia may not manifest any overt signs of sepsis other than decreased mental status, hypothermia, glucose intolerance, and inability to tolerate dialysis because of hypotension. In such a patient, there may be little if any evidence of a hyperinflammatory phase of sepsis; instead, signs of an antiinflammatory response may predominate.

### Insights into Sepsis from Postmortem Studies

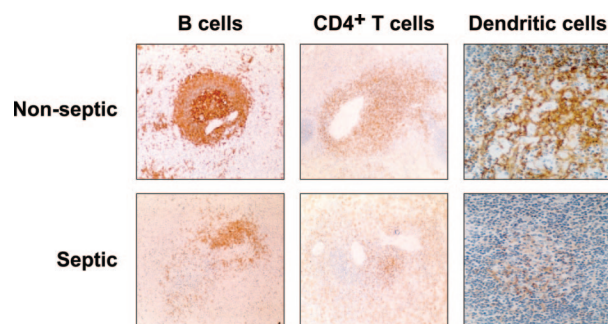
With improved treatment algorithms (see below), most patients survive the initial hyperinflammatory phase of sepsis and enter a more protracted phase of sepsis characterized by increasing immunosuppression.<sup>31,32</sup> Postmortem studies of patients who died of sepsis have provided critical insights into the mechanisms and magnitude of immunosuppression in sepsis. We performed rapid tissue harvesting at the bedside of patients dying of sepsis and demonstrated that patients

¶ Eisai Pharmaceuticals: Press release as discussed in *Wall Street Journal*, January 25, 2011.



**Fig. 1.** Immunoinflammatory response of three hypothetical patients with sepsis. The individual immune response in sepsis is determined by many factors, including pathogen virulence characteristics, size of the bacterial inoculum, patient comorbidities. The initial immune response is hyperinflammatory, but the response rapidly progresses to hypoinflammatory. In the healthy individual who experiences meningococemia, there is a robust hyperinflammatory response. Death may occur rapidly because of a hyperinflammatory state, and antiinflammatory treatments may improve survival. If infection resolves, there is only a minimal hypoinflammatory state. In the elderly patient with malnutrition who experiences diverticulitis, a prolonged hypoinflammatory response develops, followed by recovery or death. In the patient with diabetes, chronic renal failure, and pneumonia, the initial response is blunted, and there is a prolonged depression of immune function. (Modified from Hotchkiss RS, Karl IE: The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; 348:138–50. Used with permission. Copyright © Massachusetts Medical Society 2003.)

had a striking apoptosis-induced loss of cells of the innate and adaptive immune system (fig. 2).<sup>33–35</sup> The types of immune cells that are lost include CD4 and CD8 T cells, B cells, dendritic cells, and monocytes. The loss of these immune effector cells is particularly notable given that the loss occurs during severe infection, a time when clonal expansion



**Fig. 2.** Sepsis-induced loss of immune effector cells. Sepsis causes a profound depletion of cells of the innate and adaptive immune system. As shown in the color photomicrographs, sepsis induces a major loss of B cells, CD4+ T cells, and follicular dendritic cells in spleens from a patient with sepsis compared with spleens removed from critically ill non-septic patients. Magnification:  $\times 200$ . (Modified with permission from *Nat Rev Immunol* 2006; 6:813–22. Used with permission. Copyright © Nature Publishing Group 2006.)

of T cells should be taking place. Subsequent postmortem studies of pediatric and neonatal patients who died of sepsis also showed profound loss of immune cells in fatal sepsis, thereby supporting the results of the previous adult postmortem study.<sup>36,37</sup> Thus, severe depletion of immune effector cells is a universal finding in all age groups during sepsis.

It is informative to examine the impact of loss of CD4 and CD8 T cells and of monocytes or macrophages on host immunity. CD4 T cells are known as “helper” cells because they coordinate the activity of many other immune cells. For example, in response to antigenic stimulation, CD4 T cells secrete cytokines, including interferon- $\gamma$ , which induce activation of monocytes or macrophages. CD4 T cells also secrete cytokines that induce B-cell expansion, resulting in increased antibody formation. CD8 T cells help to fight infection by recognizing and inducing lysis of host cells that have become infected with intracellular bacterial or viral pathogens. CD8 T cells are also important in preventing reactivation of latent viruses. Macrophages are mature monocytes that function to activate T cells by antigen presentation. Macrophages are also professional phagocytic cells that engulf and destroy pathogens. The net impact of the loss of these various immune cells is to compromise severely the host’s ability to combat the invading pathogens.

In addition to the loss of many essential immune cells, there is an inhibitory effect of the uptake of apoptotic immune cells on the surviving cells.<sup>38,39</sup> As noted previously, the immune effector cells die by apoptosis in sepsis and are rapidly consumed by professional phagocytic cells. Although uptake of necrotic cells induces a proinflammatory response from phagocytic cells by stimulating the release of TNF- $\alpha$ , uptake of apoptotic cells induces an immunosuppressive response by inducing release of the antiinflammatory cytokines IL-10 and tumor growth factor- $\beta$ . This effect compounds the loss of the important immune cells by further compromising host immune defenses. Other mechanisms of immunosuppression that have been identified in sepsis include decreased expression of activating cell-surface molecules, such as HLA-DR, T cell “exhaustion,” and increased suppressor cells (T regulatory cells and myeloid-derived suppressor cells).<sup>40–46</sup>

Another interesting finding from a recent postmortem study done by our group is the potential role of the host parenchymal cells in modulating the immune response. New evidence indicates that endothelial and epithelial cells can express a variety of immunosuppressive molecules that are potent modulators of immune cell function.<sup>47,48</sup> The expression of these immune regulatory molecules on local parenchymal cells may explain particular organ susceptibility. In this regard, immunohistochemical staining of lungs from patients who died of sepsis showed dramatic up-regulation of the negative immunomodulatory molecule herpes-virus-entry-mediator compared on lungs from nonseptic control patients (unpublished data, R.S.H., 2011). This finding may be one explanation for the increased susceptibility of the lungs to nosocomial infection.



## Evidence of Immunosuppression in Sepsis

Careful consideration of many of the problems that occur in patients with sepsis reveals compelling evidence for immunosuppression as a major pathogenic mechanism. Here again, postmortem studies of patients who died of sepsis revealed important findings. Torgersen *et al.* reviewed postmortem findings in 235 surgical intensive care unit (ICU) patients who were admitted with a diagnosis of sepsis.<sup>49</sup> At death, approximately 80% of patients had an unresolved septic focus. Only 52 of 97 autopsy-confirmed pneumonias were diagnosed appropriately during the patients' stay in the ICU. Peritonitis also accounted for a large percentage of unresolved septic foci. The important message is that many patients in the ICU do not get better because there is still ongoing infection. Despite broad-spectrum antibiotics and aggressive source control measures, infections are not eradicated and/or new secondary hospital-acquired infections develop in many ICU patients. One key factor in the failure to eliminate the pathogens is the patients' compromised immunologic defenses. Therapies that would enhance patient immunity could prevent multiple organ failure and improve survival by assisting the body in eliminating the invading pathogens and preventing acquisition of new infections.

Other supporting evidence for immunosuppression in patients with sepsis is provided by inspection of the type of pathogens that frequently are sources of secondary infection. The secondary hospital-acquired infections include virulent organisms, such as *Staphylococcus aureus*, and those that are not particularly dangerous to nonimmunosuppressed patients (*e.g.*, *Stenotrophomonas maltophilia*, *Acinetobacter calcoaceticus-baumannii*, and *Candida albicans*).<sup>50</sup> The fact that many ICU patients ultimately die of sepsis caused by these relatively avirulent organisms highlights the profound nature of the patients' immunosuppression.

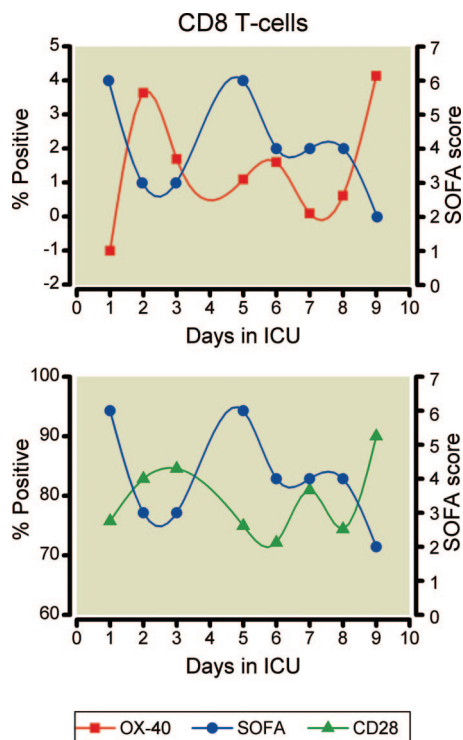
Additional compelling evidence for immunosuppression in sepsis includes studies documenting reactivation of common latent viruses. It has been recognized for a long time that immunocompromised patients (*e.g.*, patients with human immunodeficiency virus-1 or those treated with chemotherapy) experience reactivation of latent cytomegalovirus and herpes simplex virus. Similarly, recent studies in patients with sepsis have shown that a significant percentage also experience viral reactivation.<sup>51,52</sup> Limaye *et al.* examined the incidence of reactivation of cytomegalovirus in 120 critically ill patients, many of whom had sepsis.<sup>52</sup> These individuals had normal immunity before their illness. Cytomegalovirus viremia occurred in 33% of patients and was associated with prolonged hospitalization and death. In a related study, Luyt *et al.* reported a 21% incidence of herpes simplex virus bronchopneumonitis, which was attributed to viral reactivation in critically ill, immunocompetent patients requiring prolonged ventilatory support.<sup>51</sup> It is probable that only a modest number of patients in these two studies had clinically significant viral infections. Rather, these investigations support the concept that critically ill patients who have normal immunity before hospi-

talization become profoundly immunocompromised during a protracted illness, thereby enabling reactivation of latent viruses, which may become clinically relevant.

## Biomarkers as an Essential Guide to Immunotherapy

A big hurdle to the effective use of immunomodulatory therapy (*i.e.*, the use of agents that can up- or down-modulate the intensity of the host immune response) will be the ability to determine whether the patient is in the hyper- or hypoinflammatory phase of the disorder. Quantitation of circulating blood concentrations of specific markers that are indicative of the state of the patient's immune status (biomarkers) would be of enormous benefit. A recent study used just such a strategy. Patients whose circulating mononuclear cells demonstrated decreased cell expression of HLA-DR as detected by flow cytometry were treated with the immunostimulant granulocyte macrophage colony-stimulating factor (GM-CSF) to help activate and induce proliferation of existing immune effector cells.<sup>53</sup> Although it was a small phase 2 study, septic patients with low HLA-DR expression who were treated with GM-CSF had a shorter duration of mechanical ventilation and ICU and hospital stays. In addition to HLA-DR, other potential biomarkers that could be used to immunophenotype the patient immune effector cells include markers of T-cell exhaustion (programmed cell death 1 [PD-1] and PD-ligand 1) and T regulatory cells, potent inhibitors of T-cell activation. The use of phenotypic markers combined with functional studies examining the production of pro- and antiinflammatory cytokines in diluted whole blood could provide an accurate assessment of patient immune status. In this regard, a recent clinical study in pediatric patients with sepsis quantitated the production of TNF- $\alpha$  in lipopolysaccharide-stimulated blood samples. Patients with a TNF- $\alpha$  production of less than 200 pg/ml were treated with GM-CSF.<sup>54</sup> Pediatric septic patients treated with GM-CSF had restoration of blood TNF- $\alpha$  production and had a marked reduction in newly acquired nosocomial infections compared with control patients.

In addition to the expression of the monocyte human leukocyte antigen-D receptor, other potential indicators of the host immune status that might be used clinically are cell-surface expression markers on CD4 and CD8 T cells. T cells express various proteins that either augment or suppress cell activation, and this protein expression is readily assessed by flow cytometry. Our laboratory has quantitated T-cell expression of a number of these immunomodulatory proteins and correlated the expression of these markers with a measure of severity of illness called the Sequential Organ Failure Assessment score (fig. 3). Although results are preliminary, there is an inverse correlation of expression of several positive costimulatory molecules (*i.e.*, CD28 and OX40) on CD8 T cells with more severe organ failure (higher Sequential Organ Failure Assessment scores). We are also examining expression of negative costimulatory molecules on T cells. The results of these cell-surface expression studies could be combined with the results of studies of other mark-



**Fig. 3.** Temporal changes in CD8 T-cell surface markers correlate with severity of organ failure. Blood was obtained daily from a patient with sepsis, and the percentage of CD8 T cells that expressed positive costimulatory cell-surface markers CD28 or OX-40 (CD134) was quantitated via flow cytometry. To relate the flow cytometric findings to the patient's clinical course, the severity of organ failure assessment (Sequential Organ Failure Assessment) score was calculated and is depicted on the right vertical axis. Note that as the patients' Sequential Organ Failure Assessment score increases (higher Sequential Organ Failure Assessment score equates to worsened organ failure) there appears to be an inverse relationship with the expression of CD28 and OX-40. Decreased expression of these two cell-activation markers may translate into a less effective T-cell-mediated response. Quantitation of cell-surface expression of these and similar molecules may serve as "biomarkers" to allow the physician to track the activity of the sepsis and determine whether the patient is entering a hypoimmune phase of the disorder. ICU = intensive care unit.

ers of sepsis, such as procalcitonin, to provide a more global picture of host immunity. Although there are problems with the sensitivity and specificity of procalcitonin as a marker for severity of sepsis, persistently increased concentrations reflect a poor prognosis. Although any one of these markers does not necessarily reveal the overall immunologic status of a patient, it is likely that an appropriate combination of the results of multiple tests will yield more accurate assessments of immune competence, thus leading to more individualized, goal-directed therapies.

|| For the most current recommendations for the treatment of sepsis as formulated by several critical care groups, see [www.survivingsepsis.org](http://www.survivingsepsis.org). Accessed January 7, 2011.

## Advances in Current Therapy: Antimicrobial Therapy

Treatment guidelines for sepsis have been developed under the collaborative leadership of various infectious disease and critical care professional societies and are described in the Surviving Sepsis Campaign and summarized in table 1.<sup>55||</sup> Numerous studies have shown that early and full implementation of "sepsis bundles" can lead to significant improvements in patient survival.<sup>32,56–58</sup> Two key components in the successful management of sepsis are obtaining rapid control of the infectious source and providing immediate hemodynamic support to restore and maintain organ perfusion. A timely intervention to remove or reduce the infectious burden (e.g., surgical drainage) should be performed as soon as is feasible. Prompt antibiotic therapy is critical in improving survival. A key study demonstrated that for each hour that the administration of appropriate antibiotics was delayed, mortality increased by 7.6% in patients with septic shock.<sup>59</sup>

Empiric drug selection is also essential given studies documenting that failure to administer an antimicrobial with activity against the identified pathogen(s) leads to worse outcomes, including increased lengths of hospital stay and mortality.<sup>50,60–65</sup> In addition to considering the likely pathogens according to the source(s) of infection, the intensivist must consider host risk factors for drug-resistant bacteria, including previous colonization with multidrug-resistant pathogens and recent antimicrobial use.<sup>66,67</sup> Furthermore, not only is there a distinction between community-acquired infections and hospital-acquired infections, whereby hospital-onset infections generally are caused by more resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*, but patients also must be assessed for health care-associated risk factors. Residence in a nursing home or long-term care facility, recent hospitalization, attendance at a hemodialysis clinic or infusion center for the administration of chemotherapy or antibiotics, and having received hospital care at home (e.g., intravenous therapy, wound care, or specialized nursing care) are all risks factors for infections with more resistant organisms. Patients with these risk factors are commonly infected with pathogens similar to those of nosocomial infections, and failure to recognize this is frequently a cause of inappropriate therapy leading to worse outcomes.<sup>63,68</sup> Although this paradigm has been demonstrated most strongly for pneumonia, similar considerations should be made in treating infections at other sites, such as complicated intraabdominal infections and catheter-related bloodstream infections.<sup>69</sup>

The intensivist must also be aware of the institution-specific antibiogram to ensure the selection of appropriate empiric antibiotics. Development of protocols tailored to an institution can help to assure that these considerations are made when clinicians are selecting antimicrobial regimens.<sup>70,71</sup> Another strategy that can be incorporated into such protocols is the consideration for empiric combination therapy directed against resistant Gram-negative organisms until a pathogen can be iso-

**Table 1.** Summary of Surviving Sepsis Campaign Bundle Recommendations

First 6 h	First 24 h
Measure serum lactate	Administer low-dose steroids for septic shock in accordance with a standardized intensive care unit policy
Obtain blood cultures prior to antibiotic administration	Administer recombinant human activated protein C in accordance with a standardized intensive care unit policy
Administer broad-spectrum antibiotic within 3 h of emergency department admission and within 1 h of non-emergency department admission	Maintain glucose control lower limit of normal, but <180 mg/dl (10 mM)
Treat hypotension and/or elevated lactate with fluids	Maintain a median inspiratory plateau pressure <30 cm H <sub>2</sub> O for mechanically ventilated patients
If hypotension and/or serum lactate >4 mM are observed:	
Deliver an initial minimum of 20 ml/kg of crystalloid or an equivalent	
Administer vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure >65 mmHg	
Administer vasopressors for ongoing hypotension	
Maintain adequate central venous pressure and central venous oxygenation saturation	
If hypotension and/or serum lactate >4 mM persist despite fluid resuscitation:	
Achieve a central venous pressure of >8 mmHg	
Achieve a central venous oxygen saturation (ScvO <sub>2</sub> ) >70% or mixed venous oxygen saturation (SvO <sub>2</sub> ) >65%	

Adapted with permission from severe sepsis bundles. Surviving Sepsis Campaign Web site, <http://www.survivingsepsis.org/Bundles/Pages/default.aspx>. Accessed August 1, 2011. Reproduced with permission. Copyright 2011. European Society of Intensive Care Medicine, International Sepsis Forum, and Society of Critical Care Medicine.

lated and susceptibilities performed. This practice has been shown to improve the appropriateness of therapy, but the choice of agents may vary according to local susceptibilities.<sup>62,72–75</sup>

Once a microorganism has been isolated and susceptibilities determined, deescalation of the initial broad-spectrum therapy is warranted. This deescalation approach maximizes appropriate empiric antibiotic selection while minimizing antimicrobial exposure that otherwise may lead to development of antibiotic resistance, expose patients to unnecessary risk of drug toxicity, and lead to overgrowth of *Clostridium difficile*, a major ICU pathogen.

Another key facet in antimicrobial therapy is prescription of adequate dosing. A study at our institution identified underdosing of fluconazole as an independent predictor for mortality in treating *Candida* bloodstream infections.<sup>76</sup> The importance of optimal dosing is appropriately receiving more attention in recent years given both the lack of new antimicrobials in development and the observation that worse outcomes are noted among patients infected with pathogens having increased minimum inhibitory concentrations (MICs) to the chosen antimicrobial, even when remaining within the “susceptible” range. For example, by the current Clinical and Laboratory Standards Institute breakpoints, all methicillin-resistant *Staphylococcus aureus* isolates with a vancomycin MIC of  $\leq 2$   $\mu\text{g/ml}$  are considered “susceptible” to vancomycin, yet several studies have reported increased mortality among patients treated with vancomycin for an methicillin-resistant *Staphylococcus aureus* infection when the isolate has a MIC of 2  $\mu\text{g/ml}$  compared with  $\leq 1$   $\mu\text{g/ml}$ .<sup>77–79</sup> Similarly, patients infected with Gram-negative pathogens having increased MICs are reported to have increased mortality.<sup>80,81</sup> Given these findings, it may be preferred to treat such

infections with alternative antibiotics (e.g., linezolid for methicillin-resistant *Staphylococcus aureus* pneumonia) for which susceptibility testing has confirmed activity.

Another strategy being investigated to help combat the increasing challenge of drug-resistant pathogens is alteration of the antibiotic administration to optimize the pharmacokinetic–pharmacodynamic parameter that is essential for bacterial eradication. The two most commonly studied approaches are administration of  $\beta$ -lactams as continuous infusions and extended (over 3–4 h) intermittent infusions. The concept behind this strategy is to maximize the time that drug concentration remains above the MIC of the pathogen, which is the pharmacokinetic–pharmacodynamic parameter of interest for  $\beta$ -lactams. Initial Monte Carlo simulations based on pharmacokinetic data from critically ill patients have shown improved pharmacokinetic–pharmacodynamic target attainment with the application of extended and continuous infusions of piperacillin–tazobactam, cefepime, and meropenem.<sup>82–84</sup> Although limited, early clinical data suggest that patient outcomes may be improved by this approach; however, conflicting reports exist.<sup>85,86</sup> The clinical context in which this strategy makes most sense is in treating patients who are most likely to harbor pathogens with increased MICs (e.g., patients receiving recent previous antibiotic therapy or those with an extended hospital length of stay) with preserved renal function, and this population should be a focus of future investigations.

### Advances in Current Therapy: Hemodynamic Support

In 2001, Rivers *et al.* published the results of their prospective trial evaluating early goal-directed therapy in the emer-



gency department for patients with severe sepsis or septic shock.<sup>87</sup> Early goal-directed therapy, which included crystalloid resuscitation to restore preload, vasopressors to maintain adequate mean arterial pressure, and administration of blood and/or dobutamine to achieve a goal central venous oxygen saturation, produced a 16% absolute risk reduction in in-hospital mortality. Since then, early goal-directed therapy has become a cornerstone of therapy for patients with septic shock, and its components are recommended in the “Surviving Sepsis” guidelines.<sup>55</sup> Although practitioners generally agree with the concept of providing early resuscitation to achieve defined hemodynamic endpoints and optimization of organ perfusion, debate exists about the relative merit of each individual component.<sup>88,89</sup> To this end, there are ongoing studies (Australasian Resuscitation in Sepsis Evaluation Randomized Controlled Trial, Protocolized Care for Early Septic Shock trial, and Protocolised Management in Sepsis trial) attempting to investigate in more detail the potential benefits of the various components of early goal-directed therapy.

Although vasopressors and inotropes have been used for decades to support blood pressure and hemodynamic goals when treating patients with septic shock, only recently have large, randomized, controlled trials (RCTs) compared the available agents with respect to patient outcomes. In the most current Surviving Sepsis guidelines, either norepinephrine or dopamine is recommended as the initial vasopressor of choice. Epinephrine and vasopressin are not recommended as the initial vasopressor, although vasopressin can be considered as an adjunct to norepinephrine.<sup>55</sup> Recently, the CATS study group randomized 330 patients with septic shock to receive either epinephrine monotherapy or norepinephrine with or without dobutamine.<sup>90</sup> Vasopressors were titrated to achieve a mean arterial pressure of 70 mmHg, and dobutamine was added to norepinephrine when cardiac index was less than 2.5 L/min per m<sup>2</sup>. The primary outcome of 28-day mortality was not significantly different between the epinephrine and norepinephrine with or without dobutamine groups (40% *vs.* 34%, respectively, *P* = 0.31), and rates of serious adverse events including arrhythmias were similar between the groups. Arterial pH and lactate were significantly lower in the epinephrine group early in the course of therapy but were similar between groups thereafter. Thus, this trial suggests that epinephrine may be a potential alternative to norepinephrine with or without dobutamine that warrants additional study.

To follow up a retrospective study that identified dopamine administration as an independent predictor for mortality among patients with shock, the Sepsis Occurrence in Acutely Ill Patients-2 investigators performed an RCT to directly compare norepinephrine and dopamine in patients with shock.<sup>91,92</sup> A total of 1,679 patients were included: 1,044 with septic shock; 280 with cardiogenic shock; and 263 with hypovolemic shock. Overall, 28-day mortality was not different between the norepinephrine and dopamine groups (48.5% *vs.* 52.5%, respectively). In subgroup analy-

sis, mortality was similar between groups in those with septic shock but was significantly increased in those with cardiogenic shock receiving dopamine. Notably, approximately one-fourth of patients receiving dopamine had an arrhythmic event, almost double the occurrence of this adverse event in the norepinephrine group. Another recent RCT comparing norepinephrine and dopamine among 252 patients with septic shock reported strikingly similar results.<sup>93</sup>

As a result of observations that patients with septic shock often have a relative vasopressin deficiency and that administration of vasopressin subsequently improves vascular tone, there has been much interest in the use of vasopressin in this population. Given previous reports of reduced catecholamine requirements in patients with severe septic shock, the authors of the Vasopressin and Septic Shock Trial hypothesized that the addition of vasopressin (0.01–0.03 U/min) to norepinephrine (as opposed to escalating doses of norepinephrine) would lead to improved 28-day survival and that this benefit would be most apparent in those with more severe shock (more than 15 µg/min norepinephrine equivalent).<sup>94</sup> Instead, this trial of 778 patients with septic shock found no difference in 28-day mortality overall (35.4% *vs.* 39.3%,) but reported an ~11% reduction in mortality in those with less severe shock ( $\leq 15$  µg/min norepinephrine equivalent) who received vasopressin. Although these findings were in the opposite direction of the original hypothesis, laboratory models do provide a potential explanation relating to reduced vasopressin responsiveness in the septic shock state.<sup>95</sup> The findings of the Vasopressin and Septic Shock Trial lead to interesting questions warranting additional study of the role of low-dose vasopressin in less-severe septic shock and suggest that the historical practice of adding vasopressin for patients receiving high doses of catecholamine does not improve patient outcomes. Practitioners should be cautioned against the use of vasopressin in patients with moderate to severe heart failure, acute coronary syndromes, or intestinal ischemia because such patients were excluded from Vasopressin and Septic Shock Trial because of concerns about concerns.

Taken together, these trials provide support for norepinephrine as the initial vasopressor of choice (compared with dopamine) because efficacy is at least similar and there is a significantly lower risk of arrhythmias. Recent evidence suggests that epinephrine may be an alternative to norepinephrine  $\pm$  dobutamine, but given limitations of the current evidence, it remains a second-line agent. Finally, the adjunctive use of low-dose vasopressin in advanced septic shock does not appear to provide a survival benefit, but findings from the Vasopressin and Septic Shock Trial suggest a potential role in patients with less severe shock.

### The Role of Corticosteroids in Sepsis

Low-dose corticosteroids have multiple systemic effects that may mitigate sepsis pathophysiology. One effect is improvement in vascular tone that is mediated by increasing sensitiv-

ity of smooth muscle to catecholamines and reducing nitric oxide formation.<sup>96</sup> Indeed, in the two largest RCTs of corticosteroids in septic shock, the median duration of time until vasopressor withdrawal was ~2 days shorter in groups receiving steroids.<sup>97,98</sup> However, the question remains: do low-dose corticosteroids improve patient survival in septic shock? Unfortunately, the two RCTs mentioned were different in many ways and yielded conflicting results. In the previous study by Annane *et al.*, a more severely ill patient population was enrolled within 8 h of septic shock to receive the combination of hydrocortisone and fludrocortisone for 7 days (or placebo); the study reported a survival benefit in patients who had no response to an adrenocorticotrophic hormone test.<sup>97</sup> In the more recent Corticosteroid Therapy of Septic Shock trial, patients could be enrolled within the first 72 h of sepsis onset, most commonly had an intraabdominal source of infection, and were randomized to receive hydrocortisone tapered over 11 days or placebo.<sup>98</sup> Although the study was stopped short of the planned sample size of 800, analysis of the 499 included patients failed to demonstrate any difference in 28-day mortality, and this did differ according to adrenocorticotrophic hormone testing results. In addition, the Corticosteroid Therapy of Septic Shock trial suggested a greater occurrence of superinfection in those receiving corticosteroids, whereas the previous study did not. Therefore, it is difficult to identify a unifying interpretation of these two studies, and it is likely that in current practice we do not have the means to identify patients who are most likely to benefit from or be harmed by the administration of corticosteroids. The determining factor may be the immunologic state, as was discussed previously. Currently, the use of corticosteroids cannot be recommended as the standard of care, but it is reasonable to consider early in the course for patients with septic shock that does not respond to conventional measures and without regard to adrenocorticotrophic hormone testing. If administered, corticosteroids should be tapered as shock resolves. This is consistent with the most recent guidelines, in which the recommendation for corticosteroids was graded as weak (grade 2c).

### Activated Protein C in Sepsis

Drotrecogin alfa (activated) (DrotAA) and its place in sepsis therapy continue to be a source of great controversy.<sup>99–102</sup> The recombinant human activated Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial<sup>99</sup> generated early excitement by demonstrating a mortality benefit (6.1% absolute risk reduction, 95% CI 1.9–10.4%;  $P = 0.005$ ) with the use of DrotAA, a therapy targeting key derangements in coagulation and inflammation known to occur in sepsis. However, subsequent studies<sup>100,101</sup> have failed to demonstrate a consistent improvement in survival across various subgroups, and concerns remain regarding risk for serious bleeding and appropriate patient selection. A recent meta-analysis<sup>102</sup> that included randomized, placebo-controlled trials in both adult and pediatric populations reported no sur-

vival advantage with the use of DrotAA in the overall population or in various subgroups. Given the remaining concerns and controversy surrounding the use of DrotAA in sepsis, the ongoing PROWESS-SHOCK likely will play a pivotal role in determining its place in therapy. At the current time, evidence suggests that those most likely to benefit from DrotAA are patients with a high risk for mortality (*i.e.*, Acute Physiology and Chronic Health Evaluation [APACHE] II score  $\geq 25$ , multiple organ dysfunction) who can begin the regimen within 24 h of sepsis onset and do not have significant risk factors for bleeding (*i.e.*, significant coagulopathy, platelet count less than 30,000/mm<sup>3</sup>). In the most recent Surviving Sepsis guidelines,<sup>5</sup> the recommendation pertaining to patients with severe sepsis and a high risk of mortality has been downgraded to weak (grade 2b) and a lower strength of evidence (grade 2c) was assigned for patients within 30 days of surgery.

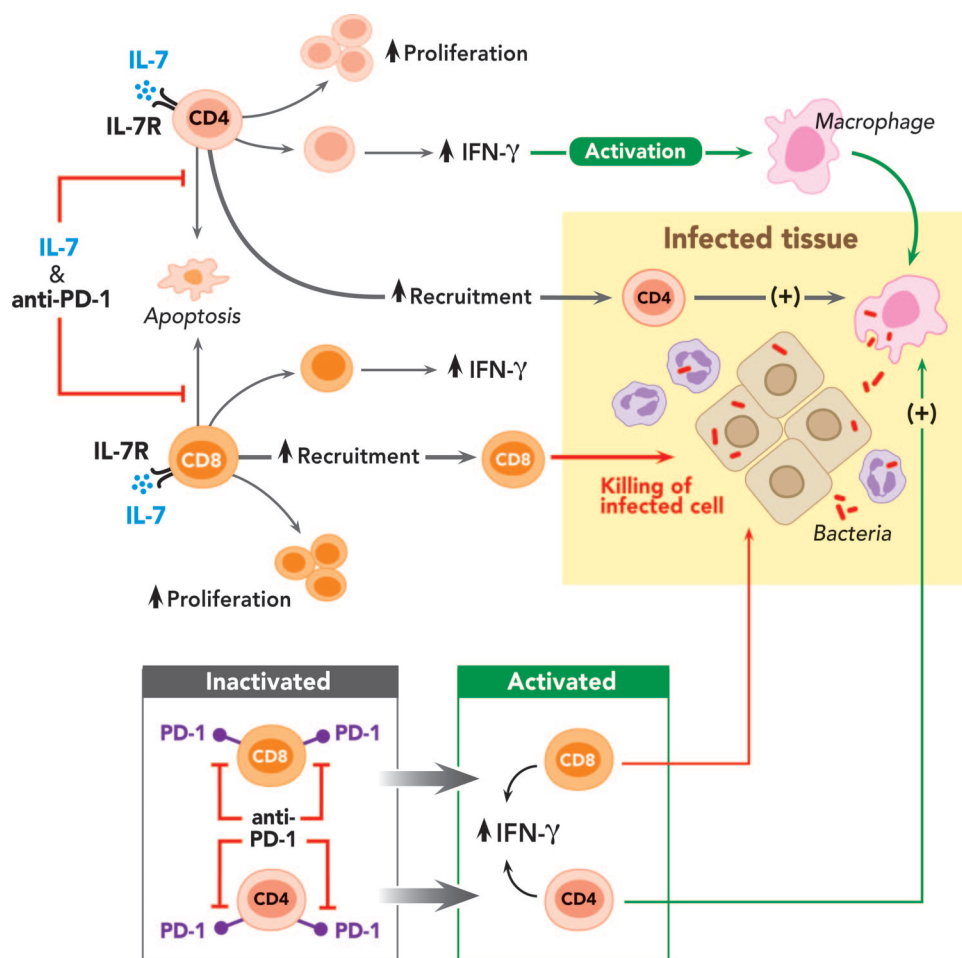
### Improving Survival in Sepsis by Immunotherapy

Given the extensive apoptosis-induced depletion of immune effector cells (fig. 2), one promising strategy is use of the anti-apoptotic, immunostimulatory cytokine IL-7 (fig. 4). IL-7 induces lymphocyte proliferation, restores lymphocyte effector function, and improves lymphocyte trafficking to sites of infection.<sup>103–106</sup> There are several studies that cumulatively provide strong theoretical support for use of IL-7 in sepsis. IL-7 restored immunity in patients with persistent viral infections and improved survival in animal models of chronic viral disease and sepsis.<sup>106,107</sup> It is currently being used in clinical trials to boost immunity in patients with chronic hepatitis C, human immunodeficiency virus, and cancer. It has an excellent safety profile and has been extremely well-tolerated.<sup>104,105</sup>

A second potential immunomodulatory therapy of sepsis involves blockade of negative costimulatory molecules present on the surface of T cells. In this regard, the recently identified receptor PD-1 has been shown to be a crucial modulator of host immune responses that is inducibly expressed primarily on CD4 and CD8 T cells.<sup>108</sup> Signaling through PD-1 inhibits the ability of T cells to proliferate, produce cytokines, or perform cytotoxic functions. PD-1 expression is increased on circulating T cells from patients with sepsis, and animal models demonstrate that blockade of this pathway improves sepsis survival.<sup>42,43</sup> Animal studies showing that blockade of PD-1 can improve pathogen clearance and current oncology trials of anti-PD-1 showing excellent clinical responses all support the potential efficacy of this drug as an effective immunomodulatory agent (fig. 4).<sup>42,43,109,110</sup>

A third potential therapy of sepsis is the use of extracorporeal blood purification. This therapeutic approach is based on the concept that the host inflammatory response can be modulated by hemofiltration to remove circulating inflammatory mediators. The basis of the theory of hemofiltration is to attenuate the inflammatory response by removing the very high peaks in proinflammatory cytokines that are pro-





**Fig. 4.** Potential immunotherapeutic approach to sepsis. Two novel approaches to sepsis include use of the immunomodulatory molecules IL-7 and anti-PD-1. IL-7 acts on CD4 and CD8 T cells to block sepsis-induced apoptosis and to cause cell proliferation. IL-7 also enables CD4 and CD8 T cells to respond to the pathogens and produce important cytokines, such as interferon- $\gamma$ , which activate macrophages. IL-7 also improves the ability of lymphocytes to traffic to the site of infection, thereby assisting in pathogen killing. Anti-PD-1 antibody is able to act on CD4 and CD8 T cells that have become inactivated or “exhausted” to restore their ability to respond to the infection. The activated lymphocytes are able to produce interferon- $\gamma$  to assist in pathogen killing. IL-7 = interleukin 7; IL-7R = interleukin 7 receptor; IFN- $\gamma$  = interferon-gamma; PMN = polymorphonuclear leukocyte; PD-1 = programmed cell death 1.

duced. In addition, antiinflammatory cytokines will be removed. This approach has some advantages in that the cytokines are not completely blocked by this method; they are only decreased in concentration. Recent progress in the design of hemofiltration filters and dialysis equipment has improved the ease and efficiency of hemopurification. Several groups have reported improved clinical findings and decreased circulating cytokines in septic patients undergoing hemopurification.<sup>111,112</sup>

### Anesthetic Management of the Septic Patient

Most of the previously discussed principles relating to the treatment of patients with sepsis are readily applicable to septic patients who require surgery. Thus, only a brief discussion of selected aspects of the anesthetic management of septic patients is provided here. The priority of management

of septic patients is always the ABCs of resuscitation. First, ensure that the patient is stable to transport to the operating room. If the patient is not already intubated, secure the airway if there is any question that the patient might not tolerate transport. Central venous access often is appropriate for several reasons, including quantitation of central venous pressures to ensure adequacy of volume resuscitation, determination of central venous oxygen saturation (as recommended by the Society of Critical Care Medicine’s Surviving Sepsis Campaign), and for administration of vasoactive agents such as norepinephrine if shock is present. Large-bore venous access and an arterial line often are required for expeditious volume resuscitation and for beat-to-beat quantitation of arterial blood pressure, respectively. Antibiotics should be administered as soon as possible if that has not already been done in the ICU or emergency department.

Before anesthetic agents are administered, the anesthesiologist should be certain that the patient has been adequately volume resuscitated. Many anesthetic agents will decrease preload (by increasing venous capacitance), decrease myocardial contractility, and/or decrease sympathetic tone, which will result in a precipitous decrease in arterial blood pressure during induction. Spinal or epidural local anesthetics cause abrupt loss of sympathetic tone, which may result in profound hypotension in the septic patient. Thus, the preferred method for anesthetizing the septic patient for abdominal or thoracic surgery usually is general anesthesia. In addition, septic patients often have abnormalities in their coagulation system, which may preclude the use of spinal or epidural anesthesia. However, in selected cases, regional anesthesia may be indicated. Although numerous laboratory studies have shown that anesthetics can modulate the immune response, most of the studies are *in vitro* or in animal models of questionable clinical relevance. Therefore, at the current time, no particular agent is recommended for modulation of the host immune response to sepsis.

Because of the effects of sepsis in delaying gastric emptying and thus increasing the risk of aspiration, the patient with sepsis should be considered to have a "full stomach." In the rare cases in which the septic patient is hypertensive during the operation, short-acting antihypertensive agents should be used to control blood pressure because hypotension may ensue rapidly. Septic patients frequently experience pulmonary complications, including adult respiratory distress syndrome. Positive end-expiratory pressure is helpful in maintaining lung volumes and improving oxygenation.

## Conclusion

In the future, immune based therapies in sepsis likely will be individualized based on particular laboratory and/or clinical findings (e.g., the use of GM-CSF based on monocyte HLA-DR expression). Similarly, flow cytometry studies that quantitate T-cell expression of PD-1/PD-ligand 1 or rapid whole-blood stimulation assays of cytokine secretion could be used to guide immunomodulatory therapies. Finally, patients with infections caused by opportunistic pathogens (e.g., *Stenotrophomonas* or *Acinetobacter*) or patients with cytomegalovirus or herpes simplex virus viral reactivation are obvious candidates for immune-enhancing therapy. Although it is conceivable that immune-stimulatory therapies could worsen the hyperinflammatory phase of sepsis or induce autoimmunity, clinical trials of interferon- $\gamma$ , a potent immunostimulatory agent, granulocyte colony-stimulating factor, and GM-CSF in patients with various systemic inflammatory states, including sepsis and trauma, did not demonstrate these types of adverse effects. In addition, most patients with refractory sepsis are so significantly immunosuppressed that they are less likely to develop hyperinflammation.

In summary, sepsis can be considered a race to the death between invading pathogens and the host immune response, and the pathogens seek an advantage by disabling selected

aspects of host defenses, including inducing apoptotic death of immune cells, decreasing monocyte major histocompatibility complex class-2 expression, increasing expression of negative costimulatory molecules, inducing antiinflammatory cytokine production, and increasing suppressor cells. Advances in immunology and in understanding the pathophysiologic basis of sepsis provide new therapeutic opportunities. Carefully designed trials of immunostimulatory agents in patients with demonstrable immunosuppression should be undertaken. Many potentially beneficial immunomodulatory agents are in clinical trials for other indications and have reasonable safety profiles. We hypothesize that an immunomodulatory approach would have wide-ranging effects and could represent a major advance in the field of infectious disease.

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