Sepsis and septic shock represent the thirteenth leading cause of death in the United States. It has been estimated that there are 500,000 new episodes each year, with an associated crude mortality of 35% [1]. Over the last 4 decades the age-adjusted mortality has climbed steadily from 0.5 to 7 per 100,000 episodes [2]. Approximately one-third to one-half of patients who are septic have culture-positive blood, and much of our understanding of this clinical syndrome derives from studies of nosocomial bacteremia and candidemia.

Several approaches have been used to study the direct impact of bloodstream infections—and therefore of sepsis—apart from the impact of patients’ underlying diseases. The first includes the use of models such as logistic regression to adjust for underlying illness and to provide estimates of relative contribution to mortality from an individual-patient viewpoint. Risk ratios or odds ratios are provided in such analyses. A risk ratio of three among patients with bloodstream infections suggests that their risk of dying is three times greater than that expected from the underlying diseases alone.

The second approach is to examine from a population viewpoint the absolute impact of the infection by subtracting the crude (overall) mortality among tightly matched controls without bloodstream infection from the crude mortality for cases of bloodstream infection. The difference is called the attributable mortality. For example, if mortality among patients with bloodstream infection, also predicts mortality. Seven published studies have examined attributable mortality [3–9], which is ~15% for coagulase-negative staphylococcal bloodstream infections, 25% for gram-negative rod infections, 30% for enterococcal infections, and almost 40% for candidal bloodstream infections (figure 1). An overall estimate of attributable mortality is 25%, when all organisms are considered.

Recently, the somewhat vague and ambiguous term sepsis has been replaced by terms for three clinical syndromes defining a progressive increase in the systemic inflammatory response to infection. An initial systemic inflammatory response syndrome (SIRS) has been defined as well as the three hierarchical stages associated with infection: sepsis, severe sepsis, and septic shock (table 1). The goal of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference group in creating new categories [10] was to provide more precise definitions to apply both at the bedside and in clinical trials.

The first epidemiological study of SIRS recently provided data supporting the clinical progression of SIRS from sepsis to severe sepsis and septic shock [11] (table 2). Progressive increases in end-organ failure, positive blood cultures, and mortality were seen with each hierarchical stage of sepsis. Moreover, 44%–71% of the cases of sepsis in any single stage had progressed from the previous stage. Thus, for the first time we have working definitions that can be applied to studies of end-organ failure after sepsis, to an understanding of the chemical derangement and molecular and cellular responses occurring at different stages, and to clinical trials of new agents to treat sepsis.

Organ Failure in Sepsis

It can be argued that until the advent of critical care, and the ability to sustain life after severe insults, there was little opportunity for organ failure. Thus, organ failure could be viewed as an iatrogenic event, the result of advances in medical support systems.

As sepsis advances toward the systemic inflammatory stage of shock, there is increased sympathetic tone, giving rise to tachycardia associated with hypotension. By reflex there is an increase in respiratory drive, and patients experience tachypnea...
In addition, an increased sympathetic tone gives rise to release of acetylcholine, which stimulates diaphoresis. Hypoperfusion of the liver and periphery lead to profound lactic acidosis, which is one of the criteria for severe sepsis. Although mental status changes such as agitation may be due to increased levels of catecholamines, stupor or coma is likely to be due to CNS hypoperfusion. In addition, an increased sympathetic tone gives rise to release of acetylcholine, which stimulates diaphoresis.

When patients with sepsis are monitored physiologically, an increased cardiac output is evident as systemic vascular resistance falls. However, with low perfusion, myocardial depression occurs and cardiac output falls [12]. Thus, organ failure is best viewed as cell death due to tissue hypoperfusion. The three factors determining global blood flow are cardiac pump function, blood volume, and peripheral vasomotor tone. Cardiac pump function itself is determined by preload (end diastolic volume), afterload (left-ventricular-wall stress), heart rate, and intrinsic contractility. As vasomotor tone falls and capillaries leak in cases of sepsis, there is great need to replace intravascular volume. The major clinical point and one worth emphasizing is that underestimating the amount of fluids is a serious error in the management of septic shock. It is still not known, however, if tissue perfusion parallels cardiac output.

If fluid replacement alone fails to correct blood pressure despite a normal or elevated cardiac output, administration of a vasopressor such as dopamine or norepinephrine is indicated. It should be noted that failure of sympathomimetic agents in the presence of an adequate preload might be associated with one of four conditions: acidosis (pH, <7.3), hypocalcemia, adrenal insufficiency, or hypoglycemia [12]. Unlike phenylephrine, which does not increase left-ventricular contractility, dopamine and norepinephrine increase cardiac contractility. As a result, the increased afterload may not be as deleterious to a patient with cardiac depression as it might with use of phenylephrine. Dopamine and norepinephrine also improve vasomotor tone, a characteristic making them useful in treatment of septic shock.

Myocardial depression and altered vascular tone appear to be interrelated in septic shock and characterize the fatal course of septic shock [13]. Specifically, among 68 patients with septic shock, the left- and right-ventricular-stroke work indexes were higher for survivors than for those who died (mean values, 25 g/m² vs. 20 g/m² [left] and 6.6 g/m² vs. 4.8 g/m² [right]).

Three lines of reasoning link the manifestations of SIRS and MODS (multiorgan dysfunction syndrome) to host-derived expression of cytokines. First, elevated levels of TNF-α and IL-6 in the blood (and not at absolute levels) is highly predictive of the ultimate development of MODS and/or of death [18]. Thus, inflammation can be considered as a cytokine-regulated process that is both essential for normal host defense and detrimental to bodily function. Serum cytokine levels in humans with septic shock have been measured and the relationship between cytokine levels and organ failure studied [18]. It was shown that among 52 patients with septic shock, the TNF and IL-6 levels both were elevated and remained so in patients with multiple-system organ failure or who died. This observation was much more useful than peak cytokine levels in predicting a poor outcome for those with shock [18]. Patients with cirrhosis, known to have difficulty clearing cytokines, also had elevated circulating cytokine levels and died at a much higher rate than did those without cirrhosis. Thus, there is some evidence that persistence of the systemic inflammatory response, rather than the magni-

Table 1. Consensus conference group definitions of the stages of sepsis.

<table>
<thead>
<tr>
<th>I. Systemic inflammatory response syndrome (SIRS)</th>
</tr>
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<tbody>
<tr>
<td>Two or more of the following:</td>
</tr>
<tr>
<td>(1) Temperature of &gt;38°C or &lt;36°C</td>
</tr>
<tr>
<td>(2) Heart rate of &gt;90</td>
</tr>
<tr>
<td>(3) Respiratory rate of &gt;20</td>
</tr>
<tr>
<td>(4) WBC count of &gt;12 × 10⁹/L or &lt;4 × 10⁹/L or 10% immature forms (bands)</td>
</tr>
</tbody>
</table>

| II. Sepsis |
| SIRS plus a culture-documented infection |

| III. Severe sepsis |
| Sepsis plus organ dysfunction, hypotension, or hypoperfusion (including but not limited to lactic acidosis, oliguria, or acute alteration in mental status) |

| IV. Septic shock |
| Hypotension (despite fluid resuscitation) plus hypoperfusion abnormalities |
Table 2. Morbidity and mortality associated with the systemic inflammatory response syndrome (SIRS).

<table>
<thead>
<tr>
<th>Variable</th>
<th>SIRS</th>
<th>Sepsis</th>
<th>Severe sepsis</th>
<th>Septic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>2-6</td>
<td>6</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Diffuse intravascular coagulation</td>
<td>8-19</td>
<td>16</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>9-19</td>
<td>19</td>
<td>23</td>
<td>51</td>
</tr>
<tr>
<td>Shock</td>
<td>11-27</td>
<td>20</td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>Positive blood cultures</td>
<td>. .</td>
<td>17</td>
<td>25</td>
<td>69</td>
</tr>
<tr>
<td>Mortality</td>
<td>7-17</td>
<td>16</td>
<td>20</td>
<td>46</td>
</tr>
</tbody>
</table>

NOTE: Table is adapted from [11].

titude of the initial response, is most important in determining organ failure.

Although single organ failure may represent isolated organ dysfunction, in SIRS it often reflects organ-specific expressions of this systemic process. Thus, it is not surprising that mortality associated with acute respiratory distress syndrome (ARDS) or acute renal failure that occurs in the setting of sepsis has not decreased measurably over the past 30 years [19–22]. Complicating our understanding of these interactions is our knowledge that artificial organ support for ARDS and acute renal failure may damage the supported organ’s function. Barotrauma commonly occurs in ventilator-dependent patients with ARDS because of overdistention of aerated lung units [23, 24]. Hemodialysis, if associated with intravascular volume removal, may make an oliguric patient anuric. Even parenteral alimentation, by enabling the bowel to rest, induces intestinal mucosal atrophy; this decreases gut barrier function and promotes bacterial colonization of the stomach with gram-negative bacilli.

Furthermore, artificial organ support damages remote organ function as well. Repetitive lung overdistention leads to release of cytokines from the lung and MODS in animal models [24], causing remote organ dysfunction. Dialysis not only exposes the patient to systemic anticoagulation but may activate polymorphonuclear leukocytes in the blood passing over dialysis membranes, which then impact in the lung microvasculature. Finally, toxic substances from the gut may directly damage the vascular endothelium system-wide [25, 26]. If MODS is a manifestation of an uncontrolled and persistent systemic inflammatory process, then therapies that only support vital organ function—without reversing the systemic inflammatory response—might prolong the dying process rather than prevent it.

Molecular Events Occurring in Sepsis

It has been recognized for some time that bacterial endotoxins initiate the syndrome of sepsis associated with gram-negative rod infection. The lipid A portion of the lipopolysaccharide (LPS) is a disaccharide with polar phosphates that are especially important. Acting at picomolar to nanomolar concentrations, bacterial LPS stimulates phagocytes, endothelial cells, and other cells.

Currently, two biochemical elements are known to recognize LPS (figure 2): an LPS-binding protein (LBP), which is an acute-phase reactant, and a receptor known as CD14. The latter can be membrane-bound or soluble [27].

CD14 is anchored in the cell membrane of monocytes and macrophages as a glycosylphosphatidylinositol (GPI)-tailed protein. Since the GPI tail does not traverse the entire cell membrane, how does signal transduction occur? Current data suggest that the nature of the membrane anchor is not essential. Instead, it is more likely that the LPS-CD14 binding leads to an interaction of some portion of CD14 protein with another cell membrane component [28, 29].

Studies performed during the past 5 years have shown that both GPI-anchored CD14 and soluble CD14 bind LPS; in both cases LPS-CD14 interactions are markedly facilitated by LBP, which acts as a transfer protein [28, 30]. The consequence of LPS binding to CD14 is cell activation, which leads to new gene expression. Binding of LPS to GPI-anchored CD14 also results in rapid translocation of LPS from the cell membrane

Figure 2. A model depicting interactions of bacterial endotoxin (lipopolysaccharide, LPS) with cells mediated by LPS-binding protein (LBP), glycosylphosphatidylinositol-anchored CD14 (mCD14) or soluble CD14 (sCD14). These interactions lead to cell activation characterized by release of mediators such as interleukin-1 (IL-1) or tumor necrosis factor (TNF) that subsequently amplify LPS-dependent host responses.
be the target of a novel group of antiinflammatory molecules ERK family of proteins [34]. Most important, p38 appears to result in activation of another group of MAP kinases, the mitogen activated protein (MAP) kinase family [30]. This process is blocked by a reduction in the biosynthesis of cytokines like IL-1 and TNF. Most investigators agree that of the cyclic imidazole family [35]. The consequence of blocking p38 activity is a marked reduction in the biosynthesis of cytokines like IL-1 and TNF. Most investigators agree that CD14 functions as a ligand-binding protein of a multimeric LPS receptor involved in cell signaling as well as a surface protein mediating internalization of LPS [17]. For the latter function the existence of a transmembrane protein has been postulated but not yet identified [29]. A model reflecting the functions of CD14 as an LPS receptor is shown in figure 3.

Progress from basic research into receptor-dependent mechanisms of LPS-induced cell activation has revealed several potential new targets for consideration with regard to sepsis. These include CD14 and p38 or other members of the MAP kinase family. Additional studies are warranted, especially because recent data also suggest these proteins play important roles in cellular responses to products of gram-positive bacteria.

Disappointment with Initial Intervention Studies

With the limited success of antibiotics in reducing mortality related to sepsis and septic shock to a very low level, it was encouraging to imagine interrupting the systemic inflammatory response to infection. The initial success of serum containing polyclonal antibody to LPS [36] and a simplified, linear concept of the sepsis cascade led to the development and clinical trials of monoclonal antibody to endotoxin [37, 38]. Subsequently, new immunotherapies were employed, including the use of IL-1 receptor antagonist, monoclonal antibodies to TNF, and TNF receptors linked to IgG [39–42]. So far, no compelling data exist to enable recommendation of any particular immunotherapy [1, 43], but some studies are still ongoing.

Two antiendotoxin monoclonal antibodies have been studied: HA-1A and E-5 [38, 39]. The initial report concerning HA-1A was encouraging in that a subset of septic patients with bacteremia appeared to have benefited from the antibody. The initial report concerning E-5 indicated that the subset of patients (bacteremic and nonbacteremic) who were not already in shock appeared to have benefited. It was perplexing that the subsets were different in the two studies, but the risks of post-hoc and unplanned subset analyses [1] became evident when follow-up studies of both products in their respectively defined subsets failed to show benefit [44]. In the second E-5 trial a new subset of patients—not already in shock, yet showing evidence of organ hypoperfusion abnormalities—appeared to have benefited. A third study of E-5, involving patients defined by the new subset, is under way.

Post-hoc subset analyses often suffer from problems with bias or confounding. In the HA-1A trial at least part of the explanation for the apparent benefit was confounding: more controls (placebo recipients) than cases (HA-1A recipients) received inadequate antibiotic therapy [43]. Correcting for appropriate antibiotics led to no observed benefit of HA-1A [44].

The phase II trial of IL-IRA showed great promise, as it demonstrated a dose-response curve in which the higher dose of IL-IRA led to the lowest mortality. However, the study was not blinded, despite being randomized and controlled. Previous analyses had suggested the development of bias in such un-
blinded studies, and, unfortunately, the phase III study showed no benefit from IL-1RA when the study groups were randomized and when both investigators and subjects were blinded to specific therapy [41]. It is interesting that a subset with an anticipated high mortality appeared to benefit, but a third trial of cases meeting that subset definition failed to show benefit (New York Times, 19 July 1994).

TNF-α has both a p55 and a p75 soluble receptor. Early studies of the latter showed no benefit in septic patients, but studies of the former are still ongoing. Some optimism for use of the p55 construct is based on the fact that, unlike the p75 product, p55 in vivo does not undergo dissociation with TNF.

What has become painfully obvious in the years since the introduction of anti-endotoxin monoclonal antibodies is that the sepsis biochemical cascade is much more complex than initially envisaged. There is great redundancy built into an incompletely understood series of pathways, and single therapies targeting unique pathways may easily fail. Furthermore, the cytokines released in sepsis are rapidly deployed and hit their cellular targets quickly. Thus, immunotherapies—if they are to be effective—will have to be given early or perhaps administered prophylactically to patients identified to be at high risk.

References

5. Spengler RF, Greenough WE III. Hospital costs and mortality attributed to nosocomial bacteremias. JAMA 1978;240:455–8.


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1. The components of SIRS are present in association with which of the following?
   A. Fever and chills
   B. Tachycardia and hypothermia
   C. Total WBC count of 10,500/mm³, plus fever
   D. Tachypnea and headache

2. Sepsis is defined as
   A. SIRS plus hypotension
   B. SIRS plus organ failure
   C. SIRS plus evidence of infection
   D. SIRS plus shock

3. Which is correct?
   A. Elevated levels of TNF-α and IL-6 are commonly seen in the blood of patients with sepsis.
   B. Absolute levels of TNF-α and IL-6 in septic patients are crudely predictive of mortality.
   C. Persistence of TNF-α and IL-6 (and not at absolute levels) is highly predictive of a poor outcome.
   D. All of the above.

4. The major component of endotoxin important in initiating sepsis after gram-negative rod infection is:
   A. LPB
   B. Lipid A
   C. KDO
   D. CD14

5. The two biochemical elements known to recognize LPS are
   A. LPB and CD14
   B. CD14 and polar phosphates
   C. GPI and CD14
   D. None of the above

6. The two anti-endotoxin monoclonal antibodies that have been studied in large clinical trials are:
   A. Anti-TNF and IL-1 RA
   B. HA-1A and E-5
   C. CD14 and GPI
   D. LPB and TNF receptor

7. If 35% of all patients with sepsis plus severe sepsis die and if 10% of a closely matched cohort without sepsis or severe sepsis die, what is the crude mortality of sepsis plus severe sepsis?
   A. 35%
   B. 25%
   C. 45%
   D. 10%

8. Given the facts above, what is the attributable mortality for sepsis plus severe sepsis?
   A. 35%
   B. 25%
   C. 45%
   D. 10%

9. Treatment of macrophages with lipopolysaccharide results in which of the following?
   A. No change in protein tyrosine phosphorylation
   B. Increased protein tyrosine phosphorylation
   C. Decreased protein tyrosine phosphorylation

10. TNF-α has
    A. Both a p55 and p75 soluble receptor
    B. Only a p55 soluble receptor
    C. Only a p75 soluble receptor