New Therapies in Sepsis*

Jean-Louis Vincent, MD, PhD, FCCP

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Despite recent improvements in intensive care monitoring, diagnostic techniques, and therapies, sepsis remains a common and critically ill condition. Moreover, related mortality rates are unacceptably high. While sepsis is an essential part of the host response to infection, an excessive response can result in tissue damage and organ dysfunction.

In the last two decades, understanding of the pathways, mediators, feedback loops, and interactions involved in the pathogenesis of sepsis and organ failure has advanced profoundly. As a result, this complex condition has become more clearly defined. With this enlightenment have come many proposed therapies, but as yet clinical trials have yielded no dramatic results, despite some encouraging animal studies. An appraisal of the design of past trials may help explain the paucity of positive results and help define criteria for future studies.

The challenge remains to identify the agent—or combination of agents—that will improve patient outcome in sepsis. Toward that effort, this article will review terminology associated with the condition, discuss current treatment options, offer possible explanations for negative trial results thus far, and present strategies to consider in developing treatment options in the future.

The Language of Sepsis

As our understanding of sepsis broadens, the terminology relating to it becomes more confusing. For the clinician, the most important term associated with the condition is infection. Indeed, sepsis is the systemic host response to infection. Although noninfectious conditions—trauma, cancer, and pancreatitis, for example—can also initiate the sepsis cascade, true sepsis requires infection. And while bacteremia is not essential for the diagnosis of sepsis, an aggressive search for infection is a crucial element of therapy.

The introduction of new terms has not been helpful. One, systemic inflammatory response syndrome (SIRS), attempts to classify patients with an inflammatory response, with or without infection.1,2 Such a definition has limitations, however. The criteria for SIRS are too sensitive; most ICU patients and many medical ward patients who do not have sepsis meet them.3,4 Moreover, many consider SIRS to be a harmful disorder. In reality, an inflammatory response may be a beneficial reaction to infection.

Current Treatment Strategies

Certain initiating factors trigger sepsis; the release and interaction of multiple mediators sustain the dynamic process. While appropriate antibiotics and surgical eradication of the source of infection are vital to patient recovery, the possibility of influencing various components of the sepsis cascade to improve outcome has inspired many clinical trials. Limiting the sepsis response—or augmenting it in cases in which it is a normal host reaction to infection—has potential benefits. We have explored these two approaches experimentally and clinically and will discuss each in more detail.

Limiting the Sepsis Response

Endotoxin Blockade: Various components of bacterial cells walls, including endotoxin, peptidoglycans, and teichoic acids, initiate the sepsis cascade. Gram-negative organisms are more classically associated with sepsis, but Gram-positive bacteria may also be responsible. Nonbacterial organisms, including fungi, viruses, and rickettsiae, can induce septic shock as well, although such microbes do not usually trigger a host response of the same magnitude.

Disruption of certain Gram-negative bacteria prompts the release of endotoxin, which activates the coagulation and complement cascades; stimulates release of many mediators, including tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, IL-8, platelet activating factor (PAF), and nitric oxide (NO); and produces the clinical symptoms and signs of sepsis. Thus, researchers have used endotoxin models to investigate the effects of endotoxin blockade on sepsis outcome. Such a blockade would likely have beneficial effects, particularly in Gram-negative sepsis.

Endotoxin, or lipopolysaccharide (LPS), is composed of three distinct regions: the O-antigen polysaccharide chain, the core oligosaccharide, and

*From the Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Belgium.

Reprint requests: Jean-Louis Vincent, MD, PhD, Dept of Intensive Care, Erasme University, Route de Lennik 808, B-1070, Brussels, Belgium.
lipid A. Investigators have identified anticore antibodies and have found that these antibodies reduce endotoxin effects and improve outcome in animal models. Baumgartner et al showed a reduction in postoperative septic shock following preoperative administration of antiendotoxin core antibodies to patients at high risk for infectious complications. Moreover, administration of a preparation that included immunoglobulin (Ig) M and IgG (Pentoglobin) to patients with septic shock and endotoxemia significantly reduced mortality compared with that of control patients. Clinical studies of two antibodies to the lipid A fraction of LPS, HA-1A and E5, had varied results. Some studies found improved outcome in patients with Gram-negative bacteremia, but later trials did not confirm these results. Some trials even suggested a possible harmful effect in patients without Gram-negative bacteremia.

Other endotoxin strategies involve antireceptor antibodies and bactericidal permeability increasing protein, which has high affinity to endotoxin and neutralizes it. In animal models, both techniques have reduced mortality. Other LPS-binding proteins, including those derived from neutrophils such as CAP18 and those occurring naturally in the horseshoe crab, have been described. Polymyxin B, a cationic antibiotic, binds to the lipid A portion of LPS, but has toxicity that limits its use in humans. Immobilizing polymyxin B on hemofiltration columns to adsorb endotoxin may overcome this problem. One clinical trial found that polymyxin decreased endotoxin levels and improved cardiovascular parameters. The lipid A antagonist E5531 has been shown to suppress the effects of LPS administered to human volunteers. Monophosphoryl lipid A, another LPS analogue, has been shown to reduce mortality from endotoxin in animals and to attenuate the response to endotoxin in healthy human volunteers.

Lipoproteins are naturally present LPS scavengers, and administration of reconstituted high-density lipoproteins has been shown to improve outcome from Gram-negative sepsis in animal models.

Anti-TNF: TNF is a key mediator of septic shock. When administered to animals, TNF reproduces the hemodynamic findings of endotoxic shock. In patients with sepsis, TNF levels are related to the severity and outcome of their disease.

One possible anti-TNF strategy is to prevent TNF release. This can be achieved by the antiendotoxin measures discussed previously, by the early use of corticosteroids, or by pentoxifylline (Trental). Pentoxifylline is a phosphodiesterase inhibitor that inhibits TNF release and neutrophil activation, adhesiveness, and degranulation. In animal models of endotoxemia, pentoxifylline improved tissue oxygen extraction capabilities. In healthy human volunteers, pentoxifylline inhibited the TNF release seen after endotoxin administration. In a recent study involving 24 patients with septic shock, those who received pentoxifylline had lower TNF levels, a significantly higher systemic vascular resistance index, and a lower cardiac index than did patients given placebo.

A second strategy involves the administration of anti-TNF-α monoclonal antibodies. Experimentally, anti-TNF-α antibodies protect animals from the lethal effects of endotoxin and Gram-negative sepsis. Initial clinical studies found that murine monoclonal antibodies to TNF-α are well tolerated, and results from a pilot study showed improved cardiac function in patients with sepsis following anti-TNF antibody administration. These findings suggest that these agents may improve patient hemodynamic status (Fig 1). Thus, two multicenter phase II/III trials in patients with sepsis using the antibody BAY x 1351.

In the first trial, called the North American Sepsis Trial I (NORASEPT), patients received either 7.5 or 15 mg/kg of the antibody or placebo. An interim report indicated that while nonshock patients had no benefit from treatment, shock patients showed a nonsignificant trend toward reduced mortality in both treatment groups compared with those who took placebo. Interestingly, the 3-day mortality rate decreased significantly, but this advantage was less obvious by 28 days. The second trial, or the International Sepsis Trial (INTERSEPT), followed a similar protocol but used an antibody dose of either 3.0 or 15 mg/kg. When the interim results from NORASEPT became available, further enrollment

![Figure 1](http://example.com/figure1.png)

**Figure 1.** Improvement in left ventricular stroke work index (LVSWI) during the first 8 h after administration of anti-TNF antibody; mean ± SD. Asterisk represents p<0.05. Reprinted from Vincent et al.

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of patients to INTERSEPT was limited to those with septic shock. The INTERSEPT study showed a dose-dependent decrease in circulating TNF levels. Although the results showed no overall reduction in 28-day mortality, the development of organ failure was significantly reduced. A third clinical trial designed to confirm these findings, NORASEPT II, has been completed recently.

A third strategy calls for administration of anti-TNF receptors to detoxify TNF. Soluble TNF (sTNF)-α receptors are naturally produced inhibitors of TNF-α. Results of clinical trials with sTNF, II (p75) were disappointing, showing increased mortality with higher doses. A weak combination of the receptor and TNF, resulting in prolonged exposure to TNF, is the most likely explanation for these findings. Ongoing clinical trials may prove sTNF receptor I(p55) to be more promising.

**Anti-IL-1:** IL-1ra, a normally occurring protein, inhibits the attachment of IL-1 to its receptor membranes. This IL-1 receptor antagonist has been synthesized by recombinant and used in experimental and clinical trials. Animal models of septic shock show decreased levels of proinflammatory cytokines, improved hemodynamic parameters, and reduced mortality in treated groups. These findings prompted the design of several clinical trials. An initial study in 99 patients with severe sepsis suggested a dose-dependent reduction in mortality. A later study showed no overall statistically significant increase in survival, although a subgroup of patients with organ dysfunction or a predicted mortality >24% did show a dose-related increase in survival. A third trial was stopped, because no effect was observed.

**Anti-PAF:** Good results from experimental trials with PAF antagonists formed the basis of several clinical trials. One study in 262 patients with severe sepsis treated with PAF antagonists showed reduced mortality in the subgroup with Gram-negative infection. Later studies with PAF antagonists failed to support these findings, however, showing no significant reduction in mortality.

**Anti-inflammatory Corticosteroids:** Corticosteroids inhibit a variety of inflammatory responses, including TNF, the arachidonic acid cascade, and NO formation via inducible NO synthase (NOS). Findings from large-scale clinical trials show that corticosteroid administered to patients with sepsis fails to decrease morbidity and mortality, however. Several nonsteroidal anti-inflammatory agents have produced beneficial results on cardiovascular parameters and outcome in animal models. In a multicenter North American trial, the cyclooxygenase inhibitor ibuprofen decreased fever but had no effect on outcome.

During sepsis, thromboxane, which promotes platelet aggregation and vasoconstriction (especially pulmonary), is released in large quantities. In a study of 54 patients with sepsis, oral administration of ketocazole, a thromboxane synthetase inhibitor, reduced the incidence of ARDS and mortality. In additional trials, however, other thromboxane synthetase inhibitors have not been found to be effective.

The administration of prostaglandin (PG) improves tissue perfusion and oxygen extraction in animal models in sepsis; it may also have beneficial effects in human sepsis. When administered to patients with ARDS, PGE, had no significant effects on survival. Findings from a phase II clinical trial showed that liposomal PGE, was associated with improved oxygenation, decreased ventilator dependency, and a trend to decreased mortality. Further trials are ongoing.

**Anti-inflammatory Cytokines:** In addition to IL-1ra, the body produces several other anti-inflammatory mediators, including IL-4 and IL-10. When administered to mice, IL-10 reduces TNF levels and endotoxin lethality. In human volunteers, recombinant IL-10 diminishes the effects of endotoxin. Although no data on the clinical use of IL-10 are available (to my knowledge), the potential role of anti-inflammatory mediators merits further attention.

**Antioxidants:** N-acetylcysteine (NAC) is an antioxidant that improves oxygen extraction capabilities and cardiac function in sepsis in experimental studies. In a clinical trial, NAC increased gastric intramucosal pH, which was an effect related to improved survival. However, findings from a recent trial showed that treatment with NAC may depress cardiac function.

**Coagulation System Interference:** Antithrombin III is a physiologic inhibitor of coagulation. During sepsis, its levels are depleted as the coagulation system is activated. Antithrombin III also increases the release of prostacyclin from endothelial cells, which produces anti-inflammatory effects. In phase II clinical studies, antithrombin III was well tolerated, and a double-blind, placebo-controlled phase III study is ongoing.

**NO Interference:** NO has been incriminated in the hypotension and myocardial depression associated with septic shock. Inhibition of NOS by L-arginine analogues has given variable results. While NOS inhibition improves mean arterial pressure, it also lowers cardiac output, raising concerns about compromised tissue perfusion. Findings from experimental studies show that NOS inhibition may selectively reduce hepatosplanchnic blood flow and increase mortality in some animal models.

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Pulmonary hypertension, which is also an effect of NO blockade, may respond to inhaled NO used concurrently. Methylene blue inhibits the effects of NO on guanylate cyclase. In addition, patients with septic shock given methylene blue show a progressive increase in mean arterial pressure, with no fall in cardiac output or oxygen consumption. There is insufficient evidence, however, to support a recommendation for methylene blue in the clinical situation.

NO is essential for microcirculatory control, and exploration continues on the use of NO donors in sepsis to maintain regional blood flow. In an animal model, the NO donor SIN-1 was shown to be well tolerated, to increase cardiac index and superior mesenteric blood flow, and to improve cardiac function.

Hemofiltration: In animal models, the use of hemofiltration to remove circulating mediators and thus reduce their damaging effects has improved survival rates. Bellomo et al demonstrated that hemofiltration removed TNF-α and IL-1 from the circulation of patients with sepsis, but Matamis et al could demonstrate no beneficial hemodynamic effects from hemofiltration. This technique is not selective; it removes all compounds, both harmful and beneficial, below a certain size. Filter size, timing, and amount of filtration are all important factors. Further studies are necessary to define the value of hemofiltration, but clinical trials are difficult to conduct. Obtaining sufficient patients for such studies requires multicenter participation, and technical variations between centers could lead to problems.

Augmenting the Immune Response

Normal functioning of the neutrophil is essential in the host response to infection. Because granulocyte colony-stimulating factor (G-CSF) stimulates production and maturation and enhances function of neutrophils, it appears to be a good therapeutic candidate in sepsis. When administered to healthy volunteers, G-CSF produces a dose-dependent rise in neutrophil levels within 4 to 5 h, with no apparent toxic effects. In experimental models of septic shock, G-CSF infusion is not only associated with improved hemodynamic status and survival but also with wors-
en ed lung injury and outcome, depending on timing, dose, and site of injection. G-CSF also appears to be a useful prophylactic option in patients at risk for sepsis. Further studies are required to identify those groups of patients who will benefit most from the use of G-CSF and to determine the optimal timing and dose of administration. Interferon-γ may also have a role in sepsis therapy by augmenting the immune response.

**PAST CLINICAL TRIALS: WHY SO LITTLE SUCCESS?**

Despite promising results from animal models and increased understanding of the pathogenesis of sepsis, attempts to influence the course of the condition have been disappointing. Several possible explanations exist.

*The results may simply reflect the ineffectiveness of the agents studied.* This seems unlikely when considering data from preclinical studies. For example, results of clinical trials with antiendotoxin antibodies vary, possibly because the related preclinical data may be inconclusive. However, other studies based on strong preclinical data, such as those using IL-1ra, have also failed to show beneficial results.

*Compensatory mechanisms may negate the effects of intervention.* The multiple feedback loops involved in the sepsis response could diminish any agent’s effect significantly. Blocking a particular mediator may be ineffective, for example, with an organism able to bypass a single obstruction. One experimental study found that while superoxide dismutase blocks the effects of oxygen-free radicals, it also increases PAF production, thus counteracting its beneficial effects. Combination therapies may prove to be more effective.

*The dose and timing of any intervention may be crucial.* The inflammatory response is, potentially, both friend and enemy. When choosing a therapy, it is vital to consider the timing and degree of sepsis blockade to ensure the most beneficial and fewest negative effects. For example, higher doses of anti-TNF antibodies fail to show any advantage on survival. Similarly, in studying the effects of sTNF receptors on endotoxemia in human volunteers, Suffredini et al found that a high dose of receptor was less immunosuppressive than a lower dose. Interestingly, the release of bound TNF was not responsible for this phenomenon. The investigators suggest that neutralization of circulating TNF activates redundant proinflammatory pathways, which may produce a mechanism of escape from the anti-inflammatory effects of the TNF receptor at high doses. For the most beneficial results, the timing of any early intervention is also important.

*The populations studied may be too heterogeneous.* This may be, in part, because of our previously limited understanding of sepsis pathogenesis and because the industry seeks an intervention with broad indications. Limiting patient populations may help in focusing therapies. For example, TNF antibodies are effective in animals with endotoxic shock but not in animals with peritonitis. Moreover, corticosteroids are ineffective in patients with sepsis yet improve outcome in patients with typhoid fe-

![Figure 3. Methods for effectively identifying patient groups for inclusion in clinical sepsis trials. CRP=C-reactive protein.](image)

<table>
<thead>
<tr>
<th>Table 2—Comparison of Morbidity and Mortality as End Points in Clinical Trials on Sepsis Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Clinically relevant</td>
</tr>
<tr>
<td>Dichotomous</td>
</tr>
<tr>
<td>Poor sensitivity</td>
</tr>
<tr>
<td>Poor specificity</td>
</tr>
<tr>
<td>Provides no information on mechanism of action</td>
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<tr>
<td>Need to define time span</td>
</tr>
</tbody>
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ver.74,75 And depending on the degree of immune responsiveness it triggers, a particular intervention may help some patients while it harms others (Table 1). While findings from studies of heterogeneous groups of critically ill patients fail to show any difference in mortality between those treated with supranormal oxygen delivery and control populations, studies restricted to surgical at-risk populations show significantly decreased mortality with treatment.76-80 Thus, interventions may prove more beneficial if they are administered to specific patient groups rather than randomly to heterogeneous groups.

The importance of mortality as an outcome is overemphasized. Because outcome involves many factors, including the existence and severity of the underlying disease process, patient age, and other therapeutic interventions, it is difficult to demonstrate a treatment's effect on mortality (Fig 2). The selection of the 28-day mortality rate may also be relevant. For example, while anti-TNF antibodies reduce 3-day mortality, this effect is no longer significant by 28 days.83 Alternatively, the 28-day mortality rate may be too short a period to assess any real effect on long-term outcome. Some may not consider lengthened survival time in a patient left with poor quality of life and in need of permanent care a treatment success.

### Developing Future Treatment Strategies: Some Considerations

Negative results from trials thus far must not be viewed as setbacks. Rather, they should encourage us to identify why previous studies failed and to find ways to improve the design of future trials. In doing this, we must remember that solid preclinical data are the foundation of clinical work. We must also agree on methods for effectively identifying patient groups (Fig 3). These methods could take several factors into consideration.

#### Genetic Predisposition

Patients with genetically determined increases in mediator production and risk of mortality may benefit more from target therapies. This group would include those homozygous for the TNFβ2 allele, who have higher TNF levels and a higher mortality rate than do heterozygous patients.81 Thus, selecting patients on the basis of genotype for anti-TNF strategies may result in more focused and effective therapeutic choices.

#### Functional Tests

In vitro stimulation tests are among the tests that may be useful in assessing host sensitivity to an inflammatory stimulus.

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**Table 3—Scoring Patients With Sepsis Using the SOFA**

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FI O₂, mm Hg</td>
<td>&gt;400</td>
<td>≤400</td>
<td>≤300</td>
<td>≤200</td>
<td>≤100</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Platelets×10⁹/mm³</td>
<td>&gt;150</td>
<td>≤150</td>
<td>≤100</td>
<td>≤50</td>
<td>≤20</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL (µmol/L)</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-5.9</td>
<td>6.0-11.9</td>
<td>&gt;12.0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>MAP&lt;70 mm Hg</td>
<td>D≤5</td>
<td>D&gt;5</td>
<td>D&gt;15</td>
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<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
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<td></td>
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<tr>
<td>MAP=mean arterial pressure; D=dopamine; Db=dobutamine; E=epinephrine; N=norepinephrine. From Vincent et al.82</td>
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<tr>
<td><strong>CNS</strong></td>
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<tr>
<td>Glasgow coma score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Creatinine, mg/dL (µmol/L) or urine output</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-3.4</td>
<td>3.5-4.9</td>
<td>&gt;5</td>
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<tr>
<td></td>
<td>(&lt;110)</td>
<td>(110-170)</td>
<td>(171-299)</td>
<td>(300-440)</td>
<td>(&gt;440)</td>
</tr>
<tr>
<td></td>
<td>&lt;500 mL/d</td>
<td>&lt;300 mL/d</td>
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<td></td>
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</tr>
</tbody>
</table>

*SOFA=sepsis-related organ failure assessment; FI O₂=fraction of inspired oxygen; MAP=mean arterial pressure; D=dopamine; Db=dobutamine; E=epinephrine; N=norepinephrine. From Vincent et al.82

1 Adrenergic agents administered for at least 1 h (doses given in µg/kg/min).
**Sepsis Markers**

The diagnosis of myocardial infarction does not rely solely on the presence of chest pain. It also requires characteristic findings from an ECG and biochemical tests. Likewise, we need to develop markers of the disease process in sepsis.

**Outcome Should Consider Both Mortality and Morbidity**

While mortality is an important measure of outcome, experts are increasingly recognizing morbidity as another valid measure of treatment efficacy (Table 2). As an example, if surfactant reduces a patient’s need for mechanical ventilation but does not affect mortality, it is still considered effective treatment. It is important to remember that improved morbidity alone is not a sufficient finding, however. A trend toward improved outcome is also necessary. Conversely, if surfactant reduces ventilation requirements yet produces serious systemic effects and increases mortality, it is no longer considered effective. Recent scoring systems, such as the sepsis-related organ failure assessment (Table 3), could be useful for monitoring the effects of interventions on disease progress and morbidity.\(^{52}\) In fact, several ongoing clinical trials use this scoring system in their protocol.

**Combination Therapies**

Because the sepsis network is complex, involving multiple feedback mechanisms, consider combination therapies. Before combining therapies, however, we must establish the independent value of each intervention. As a caveat, some experimental studies with combination therapies demonstrate an increased mortality.\(^{83}\)

**CONCLUSION**

Sepsis is often a fatal process. Yet, research is continually revealing new aspects of the complex septic response and raising possible therapies. Perhaps none of the compounds investigated thus far have consistently improved outcome because our research approach has been too narrowly focused. By attempting to completely block the sepsis response, we are depriving the body of an essential defense mechanism. We need to find methods to exploit the body’s defense system yet block those elements that react excessively. Because the immune response is so complicated, it is unlikely that a single agent will prove beneficial for all. Research with more homogeneous subgroups of patients may yield more positive results. Optimal timing and dose of any intervention are also crucial to outcome. Sepsis scores will enable us to better compare and group patients and to focus measures of outcome on both morbidity and mortality. The cause of infection must be removed to modify the sepsis response. Thus, aggressive pursuit of infection and its source, early appropriate antibiotic therapy, and surgical removal of infectious foci remain essential. As we search for the interventions that will improve patient mortality from sepsis, we must adjust the design and expectations of future clinical trials. With such an approach, we can expect positive advances in the treatment of this devastating disease process.

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