Gram-negative sepsis remains an urgent medical problem, with more than 200,000 cases occurring each year in the United States and an associated mortality rate of 20 to 50 percent. Since the onset of shock greatly worsens prognosis and to encourage early intervention, the term sepsis syndrome was developed to describe the features of a preshock septic state. Early clinical and metabolic indicators are discussed, and current therapy is reviewed. Better understanding of the pathophysiology of endotoxin release from Gram-negative bacteria and advances in biotechnology have led to the development of potential new treatments for sepsis. One such development—monoclonal antibodies to endotoxin—has shown great promise in the effort to block the progression to septic shock, reduce mortality, and decrease the overall costs of sepsis to the patient and to the national economy. (Chest 1991; 100:802-08)

**INCIDENCE AND EPIDEMIOLOGY**

The true incidence of sepsis is difficult to determine precisely because it is not a reportable disease and is often omitted as a cause of death in patients with severe underlying disease. However, it has been estimated that between 100,000 and 300,000 cases of sepsis occur each year in the United States with an associated mortality of 20 to 50 percent. As a result, septicemia is the 13th leading cause of death in the United States.

Based on national hospital discharge records, sepsis rates increased 139 percent between 1979 and 1987. Septicemia was the principal or first-listed diagnosis in more than one third of the cases. A factor believed to be involved in the higher incidence of septicemia is the increased number of immunocompromised patients resulting from improvements in medical technology. Other factors include the greater use of invasive devices, such as catheters, and an improved ability to diagnose sepsis.

Most bacteremic infections are caused by Gram-negative bacilli. *Escherichia coli* is the most commonly isolated pathogen, followed by Klebsiella-Enterobacter species. While Pseudomonas species are somewhat less frequently observed, *Pseudomonas aeruginosa* has consistently been associated with the highest mortality of all bacteremic infections.

Prior to the widespread use of modern antibiotics, Gram-negative sepsis was a rare event. For example, in their 1935 and 1941 analyses of bacteremia at Boston (Mass) City Hospital, McGowan et al. found no Klebsiella-Enterobacter isolates and only a few cases of Pseudomonas bacteremia. However, infections due to these organisms rose dramatically over the subsequent three decades, making Gram-negative bacteremia the most important infectious disease problem in US hospitals. The distributions of Gram-negative isolates and associated mortality rates summarized by Young for 11 studies covering the period 1955 to 1986 are shown in Table 1. Our center was involved in a recent prospective study of the natural
Table 1—Distribution of Gram-Negative Bacteremic Isolates Excluding Polymicrobial Infections*

<table>
<thead>
<tr>
<th>Period of Observation</th>
<th>E. coli (%)</th>
<th>Klebsiella</th>
<th>Enterobacter</th>
<th>Serratia</th>
<th>P. aeruginosa</th>
<th>Proteus species</th>
<th>Total Episodes/Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963-1986</td>
<td>63</td>
<td>9</td>
<td>12</td>
<td>34</td>
<td></td>
<td></td>
<td>129 (12)</td>
</tr>
<tr>
<td>1981-1983</td>
<td>38</td>
<td>8</td>
<td>16</td>
<td>33</td>
<td></td>
<td></td>
<td>83 (17)</td>
</tr>
<tr>
<td>1975-1977</td>
<td>76</td>
<td>(35)†</td>
<td>25</td>
<td>48</td>
<td></td>
<td></td>
<td>22 (72)</td>
</tr>
<tr>
<td>1966-1974</td>
<td>127 (38.6)</td>
<td>233 (31.8)</td>
<td>67 (35.8)</td>
<td>37 (32.4)</td>
<td>74 (68.9)‡</td>
<td></td>
<td>30 (36.7)</td>
</tr>
<tr>
<td>1965-1974</td>
<td>189 (19.5)</td>
<td>74 (24.3)</td>
<td>47 (17.0)</td>
<td>11 (18.0)</td>
<td>60 (36.6)</td>
<td></td>
<td>49 (16.3)</td>
</tr>
<tr>
<td>1972-1973</td>
<td>86 (17.4)</td>
<td>37 (43.2)</td>
<td>4 (0)</td>
<td>27 (54)</td>
<td>21 (57)‡</td>
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<td>1967-1972</td>
<td>66 (26.4)</td>
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<td>35 (14.3)</td>
<td>8 (25)</td>
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<td>58 (18)</td>
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<td>27 (54)</td>
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<td>13 (16)</td>
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Usual rank order for frequency

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<td></td>
<td>13 (16)</td>
</tr>
</tbody>
</table>

Usual rank order for mortality

*Reprinted with permission.
†Values are numbers of isolates; mortality is in parentheses.
‡Species grouped together.
§No significant difference in rank order.

The history of Gram-negative bacterial sepsis. This investigation was conducted during the period from early 1965 to mid-1988. A total of 266 patients meeting clinical criteria for sepsis received conventional treatment in 35 tertiary care centers. Rapidly fatal, ultimately fatal, and nonfatal conditions were present in 10 percent, 36 percent, and 54 percent of patients, respectively. Gram-negative bacteria were isolated in 152 (67 percent) patients, all but one of whom received appropriate antibiotics based on minimum inhibitory concentrations (MICs). Cumulative mortalities at day 14 for patients with and without proven Gram-negative sepsis were 26 percent and 23 percent, respectively. The presence of disseminated intravascular coagulation (DIC) and adult respiratory distress syndrome (ARDS) were the variables most predictive of death by day 7.

Although the increased incidence of Gram-negative sepsis has coincided with the expanded range and deployment of antimicrobial agents, it has also paralleled the introduction of medical and surgical advances that have produced new risk factors for its emergence. These include the following: increasing use of chemotherapy and radiotherapy; more widespread employment of corticosteroids and immunosuppressive agents in inflammatory diseases and organ transplantation; greater survival of predisposed patients (including the elderly), as well as those with cancer, diabetes, major organ failure, or granulocytopenia; and the increased use of invasive devices, such as surgical prostheses, inhalation equipment, and intravenous and urinary catheters. The dynamic process leading to increased numbers of cases of sepsis, therefore, consists of an antibiotic usage pattern that promotes emergence of resistant Gram-negative strains, coupled with expanded exposure to risk factors that encourage bacterial colonization.

Signs and Symptoms

The principal signs and symptoms of sepsis syndrome are reflected in the inclusion criteria we established for a major prospective intervention study (Table 2). These include fever or hypothermia, tachycardia, tachypnea, clinical evidence of an infection site, and inadequate organ perfusion or dysfunction as expressed by at least one of the following: poor or altered cerebral function, hypoxemia, elevated plasma lactate level, or oliguria. In that investigation, we defined bacteremia as the presence of a positive blood culture obtained within 48 hours of study entry, but we did not require the demonstration of bacteremia for designation of sepsis syndrome.

Fever is the most commonly observed sign of sepsis. Pyrogenic activity is stimulated by at least three endogenous substances: interleukin 1 (IL-1), interferon alpha, and tumor necrosis factor (TNF), also known as cachectin. All of these substances increase hypothalamic prostaglandin E2 synthesis. Whether fever represents a beneficial bactericidal response to infection still remains an open question. Hypothermia occurs less frequently and is observed mainly in

Table 2—Criteria for Sepsis Syndrome*

<table>
<thead>
<tr>
<th>Clinical evidence of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal temperature &gt;38.3°C or &lt;35.5°C</td>
</tr>
<tr>
<td>Tachycardia (&gt;90 beats/min)</td>
</tr>
<tr>
<td>Tachypnea (&gt;20 breaths/min while spontaneously breathing)</td>
</tr>
</tbody>
</table>

At least one of the following manifestations of inadequate organ function/perfusion:

<table>
<thead>
<tr>
<th>Alteration in mental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia (PaO2 &lt;72 mm Hg breathing room air) (overt pulmonary disease not direct cause of hypoxemia)</td>
</tr>
<tr>
<td>Elevated plasma lactate level</td>
</tr>
<tr>
<td>Oliguria (urine output &lt;30 ml or 0.5 ml/kg for at least 1 h)</td>
</tr>
</tbody>
</table>

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very young, elderly, or chronically debilitated patients.\textsuperscript{17,18}

Cardiopulmonary manifestations of sepsis range from tachycardia and tachypnea to ARDS, which is considered a catastrophic complication.\textsuperscript{17,19,20} Hyperventilation is often noted even before the onset of fever or chills, and respiratory alkalosis is usually found in early metabolic studies.\textsuperscript{2} Arterial carbon dioxide pressure is commonly $\leq 30$ mm Hg.\textsuperscript{17} Hyperventilation tends to mask early hypoxemia, an important development that may signal the development of ARDS.\textsuperscript{17} Other early changes include an increase in cardiac output, which generally offsets decreased peripheral resistance. The peripheral vasodilation associated with the early hyperdynamic changes results in well-perfused, warm skin.\textsuperscript{17} Previously, this early stage was referred to as warm shock. As the patient deteriorated and became vasoconstricted, the condition was termed cold shock. However, these terms are outdated and should not be used. Only rarely is increased systemic vascular resistance seen as a patient progresses to the late phases of septic shock; the term refractory shock better describes the clinical state of the later stages. Refractory shock can be defined as septic shock that does not respond to conventional treatment, such as fluid replacement therapy, within a specific time interval.

Although azotemia and oliguria are common features of septic shock, they may be present in the preshock state as well. Renal insufficiency in the preshock stage usually results from acute or subacute glomerulonephritis or interstitial nephritis.\textsuperscript{17} Mild liver function abnormalities are also to be expected early in the course of sepsis, and increases in serum bilirubin levels often precede clinical signs of infection.\textsuperscript{22}

The earliest hematologic changes usually associated with sepsis are neutrophilic leukocytosis with a “left shift” and eosinopenia.\textsuperscript{17} Of the several changes that may be observed in the morphology of neutrophils, vacuolization is believed to be the most specific for sepsis.\textsuperscript{23} Serum iron levels may drop markedly shortly after the onset of sepsis, apparently as a result of an iron redistribution phenomenon that may have a protective aspect.\textsuperscript{24} The DIC syndrome, which is evident only in more serious infections, is observed more commonly in Gram-negative than in Gram-positive infections;\textsuperscript{17} thrombocytopenia alone is often an early marker of sepsis.\textsuperscript{25} In diabetic patients, hyperglycemia may be one of the first detectable signs of sepsis.\textsuperscript{17,26} Common early changes in mental status in patients with sepsis are confusion, lethargy, and obtundation,\textsuperscript{17} but agitation and bizarre behavior are observed in some patients.\textsuperscript{8}

**Pathophysiology**

The pathophysiology of Gram-negative sepsis and its progression to septic shock is complex and relates to the structure and composition of the pathogenic organisms (Fig 1). The outer membrane of the Gram-negative bacterial cell has been of considerable interest. A region of the outer bacterial membrane is now considered to be the principal cause of many of the clinical and metabolic expressions of septic shock\textsuperscript{27,28} and has thus been termed endotoxin. Generally, endotoxin is thought to be a “clump” of bacterial cell wall material containing three constituents: lipid A, a core region, and an O antigen side chain.

Endotoxin release is a common feature of all Gram-negative bacteria, with the lipid A structure preserved across various species and serotypes. This substance activates the complement cascade, producing a chain of effects that can ultimately lead to ARDS.\textsuperscript{21} It can also activate factor XII and initiate another progression of events resulting in DIC.\textsuperscript{29,30}

Many of the effects of endotoxin are believed to be mediated through its stimulation of the release of the polypeptide hormone TNF, also known as cachectin.\textsuperscript{31} The pyrogen IL-1 and several of the prostaglandins are some of the endogenous substances that can be released through this septic cascade and that can stimulate effects such as hypotension, fever, and shock (Fig 2).\textsuperscript{32-34} The profound drop in blood pressure observed in septic shock appears to be related to indirect effects of endotoxin on the kinin system\textsuperscript{35} via other mediators. Because bacterial endotoxin can be released from the cell wall during and after the organisms are killed by antimicrobial agents, a great deal of recent research into the prevention and management of septic shock has focused on development of new modalities to specifically block or moderate the harmful effects of endotoxin.

**Treatment Considerations**

The cornerstone of the clinical management of sepsis remains appropriate antimicrobial therapy and, where possible, removal of the sources of infection,
such as catheters or prostheses. Appropriate antibiotic therapy decreased the occurrence of shock and the mortality rate by approximately 50 percent. Supportive measures for sepsis syndrome depend on the clinical and metabolic problems encountered. The most obvious supportive measures, including fluid and electrolyte management to support hemodynamics and organ perfusion, are well accepted. Also, sympathomimetic amines are widely used to treat the hemodynamic manifestations of septic shock.

However, the use of a number of agents that have been employed for the serious manifestations of septic shock remains controversial despite many years of study. Corticosteroids have failed to live up to their initial promise as adjunctive therapy for septic shock, as recent trials, including our own large series, could not confirm a beneficial effect. The opiate antagonist naloxone has also been of interest because of its capacity to alter the progression of endotoxin shock in animals. A trial of this agent in patients with Gram-negative sepsis, however, did not demonstrate effectiveness. Anticoagulation with heparin for the clinical expressions of DIC is believed to be useful in some patients, such as those with thrombotic complications, but there is no evidence that it improves survival potential even if it produces a beneficial effect on DIC.

A patient with sepsis syndrome that progresses to septic shock as he or she becomes hypotensive has an increasingly poorer prognosis. (If the hypotension does not respond to fluid replacement therapy, it is referred to Table 3—Differences in Mortality Rate Depending on Presence or Absence of Shock at Study Admission.

### Table 3—Differences in Mortality Rate Depending on Presence or Absence of Shock at Study Admission

<table>
<thead>
<tr>
<th></th>
<th>Sepsis Syndrome Alone (%)</th>
<th>Shock Present at Study Admission (%)</th>
<th>Development of Shock After Study Admission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10/77 (13)</td>
<td>19/60 (32)</td>
<td>19/44 (43)</td>
</tr>
<tr>
<td>Nonbacteremic</td>
<td>8/50 (16)</td>
<td>7/34 (21)</td>
<td>9/20 (45)</td>
</tr>
<tr>
<td>Bacteremic</td>
<td>2/26 (8)</td>
<td>11/34 (32)</td>
<td>10/24 (42)</td>
</tr>
<tr>
<td>Gram (−)</td>
<td>1/16 (6)</td>
<td>8/23 (35)</td>
<td>7/16 (43)</td>
</tr>
<tr>
<td>Gram (+)</td>
<td>1/10</td>
<td>3/11 (27)</td>
<td>3/6 (38)</td>
</tr>
</tbody>
</table>

*Reprinted with permission.
†Follow-up data were available for 190 of 191 patients (mortality data not available for one patient with sepsis syndrome alone).
\(\ddagger p<0.05\).
\(\ddagger\ddagger p<0.001\), compared with sepsis syndrome alone group.
\(\S p<0.01\), compared with sepsis syndrome alone group.
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\(\S\S\S p<0.01\), compared with sepsis syndrome alone group.

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to as refractory septic shock.) In a large retrospective review by Kreger et al., the presence of shock was associated with an increase in the mortality rate of 7 percent to 47 percent. Comparative mortality rates from our prospective study are shown in Table 3. For patients with sepsis syndrome alone, the mortality rate was 13 percent. These rates rose to 28 percent and 43 percent, respectively, for patients who demonstrated shock at the time of study admission and those who developed shock later. These findings clearly underscore the need for aggressive therapeutic intervention at the onset of sepsis syndrome to maximize the possibility of preventing shock and thereby improving mortality and morbidity. Recent advances in the management of sepsis with other than antimicrobial agents are certain to have a favorable impact in this regard.

**New Advances**

Advances in biotechnology during the last decade have led to a renewed interest in the use of therapeutic antisera for the treatment of sepsis syndrome. In 1982, Ziegler et al. reported the development of an antiserum prepared by immunizing donors with the J5 mutant of *E. coli*. These investigators showed a significant reduction in mortality in bacteremic patients who received the serum compared with those who did not. The development of hybridoma technology has stimulated the preparation of monoclonal antibodies of the IgG or IgM type from high-titer serum. A clinical trial with an IgG antibody did not produce favorable results. However, monoclonal antibodies of IgM isotype have been quite promising, particularly, the cross-reactive murine monoclonal antibody E5, produced using *E. coli* J5 as the immunogen. E5 was highly effective, in comparison to other combinations of antibodies and immunogens, in preventing sepsis in mice challenged with *E. coli* or *P. aeruginosa* when antibiotics were also administered. In a double-blind study of 39 patients with sepsis, two different dose regimens of E5 were compared with placebo. The 39 patients were divided into three treatment groups: 13 patients received E5 2.5 mg/kg/day for two days; 13 received E5 7.5 mg/kg/day for two days; and 13 received placebo. Mortality was only 7 percent in all patients administered E5 plus standard therapy vs 22 percent in those who received only standard therapy.

Our center participated in a large, multicenter, double-blind trial of 486 patients with suspected Gram-negative sepsis in which E5 was compared with placebo. The results indicated that administration of E5 significantly reduced mortality from sepsis and produced significant resolution of multiorgan failure in patients with Gram-negative sepsis who were not yet in refractory shock. Results from a similar trial using human monoclonal antibodies directed against endotoxin have been reported by Ziegler et al. In this study, the empiric use of human monoclonal antibody was able to prevent death from documented Gram-negative bacteremia (positive blood culture), particularly in patients with shock. Together, these studies show that both murine and human monoclonal antibodies increase survival for patients with Gram-negative infections.
This treatment appears to be well-tolerated on the basis of early clinical results.17,40 Advances of this magnitude have the potential to substantially improve the survival of patients with sepsis syndrome and are likely also to reduce the total cost associated with the treatment of sepsis.

The future outlook for the treatment of sepsis and its complications is exciting. Some of the agents currently being investigated are shown in Figure 3. I believe that we will soon be using several agents in combination to treat sepsis, which may be more efficacious than when these agents are used singly. The risk/benefit as well as the cost/benefit of such combinations, however, will need to be assessed by careful clinical studies.

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