Letter to the Editor

Gram-Negative Sepsis: What Dilemma?

Bone reviewed the syndrome of gram-negative sepsis with an emphasis on aspects of its clinical management and the promise of antendotoxin immunotherapy (3). He suggested that the triggering of mediators by bacterial endotoxin, which antimicrobial therapy fails to address, is the basis for the continuing high mortality and complications associated with this condition.

The new terminology presented is an important step toward progress in this area, as it is based on the recognition that patient outcome in this syndrome is more closely related to the degree of organ damage than to the documentation of infection (i.e., bacteremia) by the microbiology laboratory. For example, in the Veterans Administration systemic sepsis study, alterations in mental state were a powerful predictor of outcome (odds ratio for mortality, 2.36; \( P < 0.0001 \)) whereas gram-negative bacteremia was not (odds ratio for mortality, 1.32; \( P \) was not significant \([12]\)). As a consequence, recent efforts have focused on the mediators of the sepsis cascade, with particular attention to endotoxin.

From three perspectives, however, the role of endotoxin in the sepsis syndrome is far from clear. First, the neologism “endotoxemia” emphasizes that the detection of endotoxin in blood (previously termed “endotoxemia”) does not automatically imply “toxemia” (\([10]\)).

Second, experimental data demonstrate that antibiotics do in fact induce the release of endotoxin in patients (\([5, 9]\)). However, it is difficult to find documented cases in which this release of endotoxin could be of any clinical consequence (\([6]\)).

Third, the effects of endotoxin cannot account for the multiple organ failure (MOF) paradoxes. The process may involve multiple organs; the lag period; the lack of microbiological documentation for many clinically septic patients, even those with a fatal outcome; and the lack of response to currently applied therapy (\([4]\)).

There is increasing recognition that mechanisms, such as lipopolysaccharide-binding proteins (\([11]\)), which mediate much of the response to endotoxin in sepsis, are regulated. Hence, the mass action response that follows the acute administration of endotoxin to volunteers may not accurately represent the pathophysiology of sepsis. In particular, these acute effects of endotoxin cannot explain the MOF paradoxes.

It is difficult to establish the experimental evidence on which Bone has based the assertion that monoclonal antendotoxin antibodies bind to endotoxin or neutralize its adverse effects, as much of his cited literature does not correspond to pertinent entries in his list of references. Moreover, there is now in vitro (\([13]\)) and in vivo (\([2]\)) evidence to refute this assertion. In the clinical evaluations of both E5 and HA-1A, no overall benefit was noted. Rather, the benefit was confined to subgroups of patients that were defined only in retrospect. Hence, the value of antendotoxin therapy (\([1]\)) and the mechanism of its benefit (\([7]\)) are questionable.

This is not to deny that these immunotherapy approaches may yet have an important role in that subgroup of patients which we are not yet able to identify prospectively. However, reappraisal of the concept of endotoxin suggests that its role in the mediation of sepsis is unproven, and other components of gram-negative bacteria, for example, L-forms (\([8]\)), have yet to be examined.

REFERENCES


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Author’s Reply

The dilemma that I spoke of in my article is one of both terminology and clinical trial conduct. Problems with the old terminology resulted in much confusion, as various individuals defined such a clinical entity as “sepsis” in different ways. The terms developed by the ACCP/SCCM Consensus Conference provide a standard reference and should resolve some of this confusion. The use of poorly defined terms was...
whether they met criteria for SIRS. Reproduced with permission of the publishers (1).

also an important stumbling block to clinical researchers; with inclusion criteria and disease definitions that were not comparable, and without the ability to stratify patients by the severity of illness, trial results were very difficult to interpret. Nonstandard terminology made it especially difficult to compare results from study to study. In many cases, patients with high risk did not fulfill the criteria for sepsis syndrome.

An ACCP/SCCM study group examined the risk factors and classifications of 519 patients admitted to intensive care units with a diagnosis of sepsis. Figure 1 shows that 503 of these 519 patients fulfilled the definition for sepsis inflammatory response syndrome (SIRS) and indicates their risk distributions (1). Figure 2 shows those 503 patients with SIRS stratified by mortality risk, along with their eventual mortality (1). These data demonstrate the difference that definitions can have on the results obtained by clinical trials.

The essential issue is that, because of the equivocal results obtained in clinical trials to date, we cannot use certain pharmacological agents that may, nonetheless, be effective treatments. This is a result of our inability to prospectively define the populations that might benefit from their use. To date, this factor has influenced the results of clinical trials of monoclonal antibodies to endotoxin and the interleukin-1 receptor antagonist. For example, in trials of the interleukin-1 receptor antagonist, when a population with an expected mortality of more than 25% was used, the data indicated that a significant, beneficial effect resulted from the treatment. However, this is a post hoc analysis and it could be questioned. In such a case, the enrollment of large numbers of patients with low risk would make the hypothesis of a decreased mortality difficult to prove. The same thing was seen in the results of the second clinical trial of E5, a monoclonal antibody against endotoxin. In that study, the placebo group had a lower mortality than would have been expected on the basis of previous studies.

It is hoped that future studies will use terminology that promotes the inclusion of larger numbers of patients who are appropriately stratified. This should allow us to prospectively define populations likely to benefit from this treatment and to exclude those that are less likely to benefit. Additionally, it would greatly improve our ability to interpret and compare clinical results.

REFERENCE


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