Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine.

R C Bone, R A Balk, F B Cerra, R P Dellinger, A M Fein, W A Knaus, R M Schein and W J Sibbald

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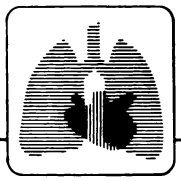

accp/sccm consensus conference

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

THE ACCP/SCCM CONSENSUS CONFERENCE COMMITTEE:
Roger C. Bone, M.D., F.C.C.P., Chairman
Robert A. Balk, M.D., F.C.C.P.
Frank B. Cerra, M.D.
R. Phillip Dellinger, M.D., F.C.C.P.
Alan M. Fein, M.D., F.C.C.P.
William A. Knaus, M.D.
Roland M. H. Schein, M.D.
William J. Sibbald, M.D., F.C.C.P.

An American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference was held in Northbrook in August 1991 with the goal of agreeing on a set of definitions that could be applied to patients with sepsis and its sequelae. New definitions were offered for some terms, while others were discarded. Broad definitions of sepsis and the systemic inflammatory response syndrome were proposed, along with detailed physiologic parameters by which a patient may be categorized. Definitions for severe sepsis, septic shock, hypotension, and multiple organ dysfunction syndrome were also offered. The use of severity scoring methods when dealing with septic patients was recommended as an adjunctive tool to assess mortality. Appropriate methods and applications for the use and testing of new therapies were recommended. The use of these terms and techniques should assist clinicians and researchers who deal with sepsis and its sequelae.

(Chest 1992; 101:1644-55)

MODS = multiple organ dysfunction syndrome; SIRS = systemic inflammatory response syndrome

An American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference was held in Chicago in August 1991 with the goal of agreeing on a set of definitions that could be applied to patients with sepsis and its sequelae. It was the goal of this conference to provide both a conceptual and a practical framework to define the systemic inflammatory response to infection, a progressive, injurious process that falls under the generalized term "sepsis" and includes sepsis-associated organ dysfunctions as well. We expect that the broad definitions proposed in this report will improve our ability to make early bedside detection of the disease possible, and thus allow early therapeutic intervention. In addition, the standardization of research protocols will be possible, as will improved dissemination and application of information derived from clinical studies. We hope that the continuing research on the inflammatory response to infection will allow us to understand the cellular and immunologic mechanisms that cause sepsis and related organ dysfunctions and, sometimes, death. We recognize the limitations of the definitions we have proposed and urge further studies to validate these clinical concepts, critical phases, and measures of inflammation by using more sophisticated risk stratification and other tools of evaluation.

For editorial comment see page 1481

Reprint requests: Dr. Bone, Rush-Presbyterian St. Luke's Medical Center, 1753 West Congress Parkway, Chicago 60612

Two other issues are also addressed in this article and serve to round out the discussion of the causes and treatment of sepsis: (1) the utilization of severity-of-illness scoring systems that allow the consistent evaluation, description, and risk prognostication of patients with sepsis; and (2) guidelines for the use of innovative therapies in severe sepsis.

Sepsis

The systemic response to infection has been termed *sepsis.*[1,2] Sepsis is an increasingly common cause of morbidity and mortality, particularly in elderly, immunocompromised, and critically ill patients.[1,3-5] Sepsis has been reported to be the most common cause of death in the noncoronary intensive care unit.[4,6] Its rising incidence, new etiologies, and appearance in new populations of patients have been related to changing demographics and the increased use of more potent and broader-spectrum antibiotics, immunosuppressive agents, and invasive technology in the treatment of inflammatory, infectious, and neoplastic diseases.[3,4] Recent clinical trials have been undertaken to evaluate both conventional and innovative therapies in the treatment of sepsis.[7-10] However, interpretations of these results have been obscured by the use of varying definitions for the following terms: *infection, bacteremia, sepsis, septicemia, septic syndrome,* and

septic shock.[7-12] An additional source of confusion has been the application of the terms *sepsis* and *septic syndrome* to noninfectious inflammatory states.[13,14] Several editorials and position papers have recently attempted to provide a framework for the standardization and simplification of this terminology.[13,15-17] To advance these processes, this consensus conference will offer recommendations for the standardization of terminology.

The standardization of terminology is necessary to eliminate confusion in communication for both clinicians and researchers concerning sepsis and its sequelae. By standardizing terms, such as *sepsis*, the ability to compare protocols and evaluate therapeutic interventions is significantly improved. The following definitions should be used as general guidelines in the design of future investigations into potential new diagnostic and treatment modalities.

Recommendation 1

The term *sepsis*, in popular usage, implies a clinical response arising from infection. It is apparent that a similar, or even identical, response can arise in the absence of infection. We therefore propose the phrase *systemic inflammatory response syndrome* (SIRS) to describe this inflammatory process, independent of its cause (Fig 1).

This systemic inflammatory response can be seen following a wide variety of insults and includes, but is not limited to, more than one of the following clinical manifestations: (1) a body temperature greater than 38°C or less than 36°C; (2) a heart rate greater than 90 beats per minute; (3) tachypnea, manifested by a respiratory rate greater than 20 breaths per minute, or hyperventilation, as indicated by a $PaCO_2$ of less than 32 mm Hg; and (4) an alteration in the white blood cell count, such as a count greater than 12,000/cu mm, a count less than 4,000/cu mm, or the presence of more than 10 percent immature neutrophils ("bands"). These physiologic changes should represent an acute alteration from baseline in the absence of other known causes for such abnormalities, such as chemotherapy, induced neutropenia, and leukopenia.

Rationale: The systemic inflammatory response is seen in association with a large number of clinical conditions. Besides the infectious insults that may produce SIRS, noninfectious pathologic causes may include pancreatitis, ischemia, multiple trauma and tissue injury, hemorrhagic shock, immune-mediated organ injury, and the exogenous administration of such putative mediators of the inflammatory process as tumor necrosis factor and other cytokines.

A frequent complication of SIRS is the development of organ system dysfunction, including such well-defined clinical conditions as acute lung injury, shock, renal failure, and multiple organ dysfunction syndrome (MODS). The term *MODS* also stems from this consensus conference, and its definition will be dis-

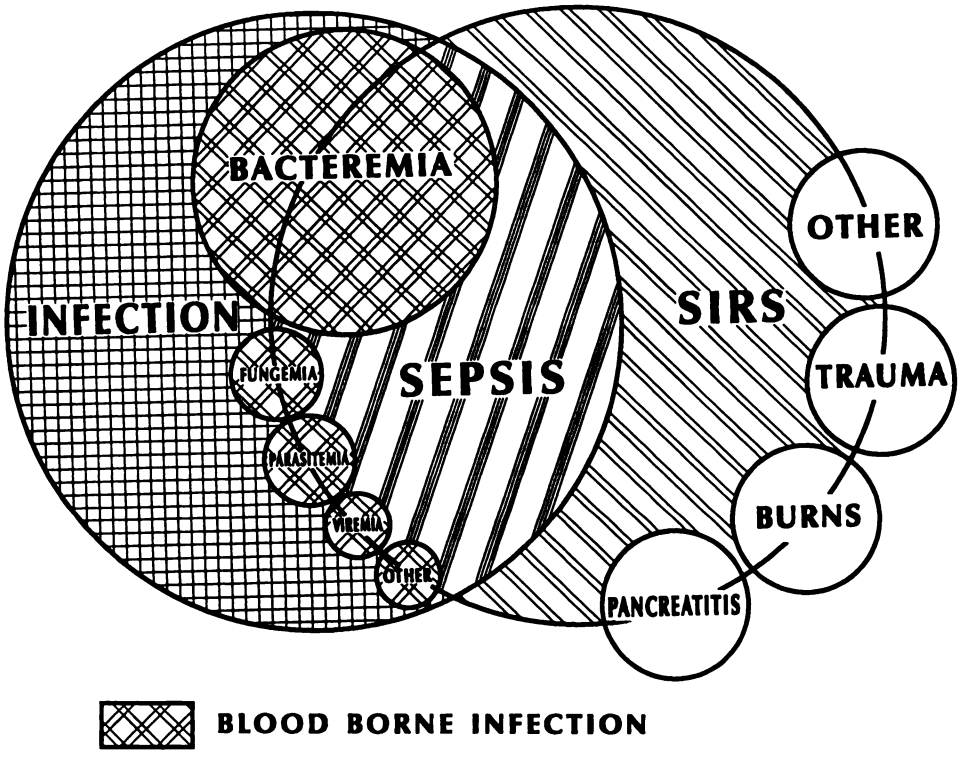

FIGURE 1. The interrelationship between systemic inflammatory response syndrome (SIRS), sepsis, and infection.

cussed later in this report.

It is likely that similar pathogenesis and pathophysiology underlie the various clinical entities that constitute SIRS. Future definitions may take into account the pathogenetic mechanism in descriptions of the response. Further work is needed to characterize the clinical and prognostic significance of SIRS and its associated sequelae.

Recommendation 2

When SIRS is the result of a confirmed infectious process, it is termed *sepsis*. In this clinical circumstance, the term *sepsis* represents the systemic inflammatory response to the presence of infection.

Rationale: Sepsis has been well recognized as a systemic inflammatory response to an active infectious process in the host. The use of a broad-based clinical definition of the septic process may facilitate studies of the pathogenetic mechanisms involved in the production of the systemic inflammatory response to infection, as well as the noninfectious causes of SIRS. An improved understanding of these mechanisms will lead to improved therapeutic management.

Recommendation 3

In an attempt to improve the written and verbal communication concerning infection as it relates to SIRS, we recommend the adoption of the following nomenclature and definitions for several commonly used terms (Table 1):

Infection is a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

Bacteremia is the presence of viable bacteria in the blood. The presence of viruses, fungi, parasites, and other pathogens in the blood should be described in a similar manner (*ie*, viremia, fungemia, parasitemia, *etc*).

Septicemia has been defined in the past as the presence of microorganisms or their toxins in the blood. However, this term has been used clinically and in the medical literature in a variety of ways, which has added to confusion and difficulties in data interpretation. Septicemia also does not adequately describe the entire spectrum of pathogenic organisms that may infect the blood. We therefore suggest that this term be eliminated from current usage.

Sepsis is the systemic inflammatory response to infection. In association with infection, manifestations of sepsis are the same as those previously defined for SIRS, and include, but are not limited to, more than one of the following: (1) a temperature greater than 38°C or less than 36°C; (2) an elevated heart rate greater than 90 beats per minute; (3) tachypnea, manifested by a respiratory rate greater than 20 breaths per minute or hyperventilation, as indicated by a $PaCO_2$ of less than 32 mm Hg; and (4) an alteration in the white blood cell count, such as a count greater than 12,000/cu mm, a count less than 4,000/cu mm; or the presence of more than 10 percent immature neutrophils. To help identify these manifestations as sepsis, it should be determined whether they are a part of the direct systemic response to the presence of an infectious process. Also, the physiologic changes measured should represent an acute alteration from baseline in the absence of other known causes for such abnormalities.

Recommendation 4

Sepsis and its sequelae represent a continuum of clinical and pathophysiologic severity. The degree of severity may independently affect prognosis. Some clinically recognizable stages along this continuum that may adversely affect prognosis include the following:

Severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension. Hypoperfusion abnormalities include lactic acidosis, oliguria, and acute alteration of mental status.

Sepsis-induced hypotension is defined by the pres-

Table 1—*Definitions*

Infection = microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
Bacteremia = the presence of viable bacteria in the blood.
Systemic inflammatory response syndrome (SIRS) = the systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or $PaCO_2$ <32 mm Hg; and (4) white blood cell count >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms
Sepsis = the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or $PaCO_2$ <32 mm Hg; and white blood cell count >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms.
Severe sepsis = sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.
Septic shock = sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Sepsis-induced hypotension = a systolic blood pressure <90 mm Hg or a reduction of ≥40 mm Hg from baseline in the absence of other causes for hypotension.
Multiple organ dysfunction syndrome (MODS) = presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

ence of a systolic blood pressure of less than 90 mm Hg or its reduction by 40 mm Hg or more from baseline in the absence of other causes for hypotension (*eg*, cardiogenic shock).

Septic shock is a subset of severe sepsis and is defined as sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction. Patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction, yet they would still be considered to have septic shock.

Rationale: Recent, large-scale, multicenter, prospective studies of sepsis have suggested that there is a continuum of severity encompassing both infectious and inflammatory components. The condition begins with infection and potentially leads to sepsis with organ system dysfunction and septic shock.[7-10] Bacteremia and hypotension may occur as a part of this process. While recognizing that the disease process forms a continuum of severity, an analysis of several clinical trials has indicated that definable phases exist on that continuum which characterize populations at increased risk of morbidity and mortality.[7-11,18-21] One such phase should be termed *severe sepsis* or *sepsis with organ system dysfunction.* Some have previously used the term *septic syndrome* to describe this phase of the septic process.[11] However, the term septic syndrome has been applied to a variety of inflammatory states and it now appears to be both confusing and ambiguous.[13,14] We, therefore, recommend that the term *septic syndrome* no longer be used.

These critical stages in the septic process are likely to have independent prognostic implications;[18,19] however, this hypothesis has not been tested in large-scale, prospective, multicenter trials. Risk assessment may be a more appropriate approach to identifying patients likely to develop morbidity and mortality. The development and refinement of such evaluation tools is encouraged. Previous studies have shown that septic shock, as defined above, is associated with increased mortality.[11,19,22]

Conclusion

We have provided both a conceptual and a practical framework for the definition of the systemic inflammatory response to infection (sepsis). The application of these broad definitions will improve early bedside detection and permit early intervention in sepsis. In addition, the standardization of research protocols will be enhanced, as will application of information derived from clinical studies. We believe that the early identification of the inflammatory response to infection will enhance our understanding of the cellular and immunologic mechanisms that can cause sepsis and organ dysfunction and, in the most severe cases, death. Because of the limitations that are inherent in these definitions, we urge further studies that utilize more sophisticated risk stratification and other tools of evaluation to validate the clinical concepts, critical phases, and measures of inflammation that are important for the clinical treatment of sepsis.

Multiple Organ Dysfunction Syndrome

The increasing incidence of morbidity and mortality caused by multiple organ failure has paralleled improvements in the life-support technologies available to patients admitted to an intensive care unit (ICU). As newer technologies for the monitoring and support of patients sustaining life-threatening critical illness became established, retrospective clinical studies found that a major threat to survival was not the underlying illness, or even a single complication thereof, but rather a process of progressive physiologic failure of several interdependent organ systems.[23-27] The terms *progressive* or *sequential organ failure*,[28] *multiple organ failure*,[25] and *multiple systems organ failure*[26] were thereby introduced to describe an evolving clinical syndrome that was characterized by the development of otherwise unexplained abnormalities of organ function in critically ill patients. The phenomenon that these terms describe is clearly increasing in prevalence, as a result not only of improvements in life-support technology (both medications and devices) but also of the application of these technologies to an increasingly high-risk patient population.

Conventional terminology is considered inadequate to accurately characterize this syndrome. Thus, clinical descriptions of the organ failure syndrome emerged in an arbitrary and retrospective fashion. Criteria for defining abnormalities of specific organ function have also been widely dissimilar from one study to another and, for the most part, have been predicated on the concept of organ *failure*, a dichotomous event that is either present or absent, rather than organ *dysfunction*, a continuum of physiologic derangements. The static criteria used in current epidemiologic descriptions preclude the possibility of dynamically changing organ function that characterizes the syndrome as it is encountered clinically. This issue, if it is not soon addressed, could potentially hinder future advances in the treatment of this syndrome.

Early clinical studies of multiple organ failure identified occult infection as the most important clinical correlate of the syndrome.[23,26,27,29] However, recent work has shown that organ system dysfunction can evolve in the absence of an untreated focus of invasive infection[30-32] and can be reproduced experimentally by the infusion of a diverse spectrum of endogenously derived mediators of inflammation.[33-36] Futhermore, recent work has demonstrated a complex

interrelationship among individual organs, such that failure of one may establish an amplification process that hastens injury to another.

Our understanding of the pathophysiology of organ dysfunction and failure in critically ill patients is improving. In contrast, descriptions of the epidemiology of this syndrome remain meager. Available reports focus primarily on disease that is severe, perhaps at a point in the disease course where interventions may no longer be anticipated to have potential for success.

The purpose of this statement is to propose a conceptual framework for future studies of the clinical phenomenon of organ system dysfunction in critical illness, and to lay the foundations for common terminology and criteria to describe the syndrome.

Recommendation 1

The detection of altered organ function in the acutely ill patient constitutes a syndrome that should be termed *multiple organ dysfunction syndrome*. The terminology *dysfunction* identifies this process as a phenomenon in which organ function is not capable of maintaining homeostasis. This process, which may be absolute or relative, can be more readily identified as a continuum of change over time. An example of relative organ dysfunction is found in the patient with a normal cardiac output and systemic oxygen delivery who exhibits evidence of inadequate tissue oxygenation (*eg*, lactic acidosis).

The proposed acronym also identifies multiple organ dysfunction as a "syndrome." In this context, MODS is proposed to describe a pattern of multiple and progressive symptoms and signs that are thought to be pathogenetically related.

Rationale: In contrast to the static descriptions that have been used previously, the proposed change in terminology emphasizes the dynamic nature of the process under discussion. Thus, the following points must be recognized:

1. MODS describes a continuum of organ dysfunction, although specific descriptions of this continuous process are not currently available.
2. The recognition of early organ abnormalities must be improved so that treatment can be initiated at earlier stages in the evolution of this syndrome.
3. Changes in organ function over time can be viewed as an important element in prognostication. When applied to MODS, existing measures of illness severity provide only a snapshot in time of this dynamic process, and are generally without reference to the natural course of the disease.
4. MODS is subject to modulation by numerous factors at varying time periods, both interventional and host-related.

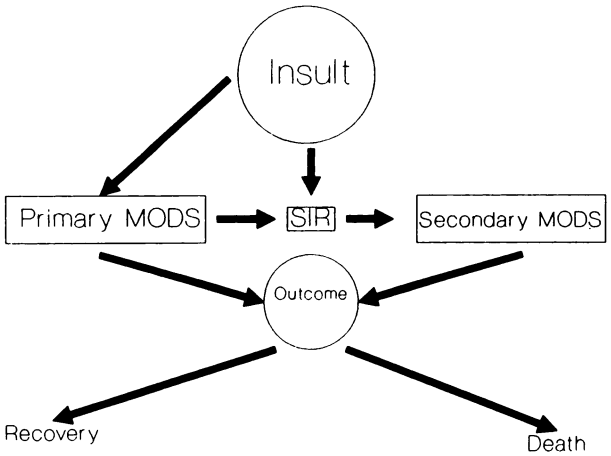

FIGURE 2. The different causes and results of primary and secondary multiple organ dysfunction syndrome (MODS).

Recommendation 2

MODS may be described as being either primary or secondary.

Rationale: MODS develops by two relatively distinct, but not mutually exclusive, pathways. Primary MODS is the direct result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself. An example of primary MODS is organ dysfunction as the immediate result of trauma (*eg*, pulmonary contusion, renal failure due to rhabdomyolysis, or the coagulopathy due to multiple transfusions). In primary MODS, the participation of an abnormal and excessive host inflammatory response in both the onset and progression of the syndrome is not as evident as it is in secondary MODS (Fig 2).

Secondary MODS develops, not in direct response to the insult itself, but *as the consequence of a host response*, and is identified within the context of SIRS. SIRS is also a continuous process, and describes an abnormal host response that is characterized by a generalized activation of the inflammatory reaction in organs remote from the initial insult. When the process is due to infection, the terms *sepsis* and *SIRS* are synonymous. Given that SIRS/sepsis is a continuous process, MODS may be understood to represent the more severe end of the spectrum of severity of illness that characterizes SIRS/sepsis. Thus, secondary MODS usually evolves after a latent period following the inciting injury or event, and is most commonly seen to complicate severe infection.

Recommendation 3

Since criteria that are universally applicable in quantifying the individual organ dysfunctions comprised by MODS cannot be proposed at this time, a comprehensive and continuously updated data base to clinically test and validate optimal criteria for describ-

ing this syndrome must be established.

Rationale: Data are insufficient to justify a recommendation of universally applicable criteria that could serve as a validated operational template. The assignment of criteria for measuring organ dysfunction should not occur *a priori*, but should result from an empiric process in which specific variables are tested against outcome. By doing so, the predicted accuracy of individual variables, groups of variables, and levels of abnormality can be defined in a manner that reflects current clinical practice.

Severity-of-Illness Scoring System

A common theme in the two previous sections of this consensus statement is that we are treating more severely ill patients at later stages of illness. It is also apparent that many of these patients who have more complex illnesses may be suffering from a combination of chronic and acute disease. The nature of disease presentation is changing, and patient or host response is exemplified by the proposed introduction of new syndromes, such as SIRS and MODS. The recognition and treatment of these syndromes would not have been possible without our advanced diagnostic and life-support capabilities. It is also emphasized, however, that patients with both of these syndromes present somewhere along a continuum of illness severity, and that an accurate description of that continuum is essential to appropriate usage of these terms.

The rationale for using scoring systems, therefore, is to ensure that the increased complexity of disease in patients currently being treated is consistently represented in evaluations and descriptions. A specific goal of severity scoring systems is to use these important patient variables to describe the relative risks of patients and, thereby, to identify where, along the continuum of severity, the patient resides.[37] This will reduce the variation due to patient factors so that the incremental impact of new or existing therapy can be more precisely determined.[38] It is also hoped that more precise measurements of patient risk will lead to new insights into disease processes and serve as a tool with which clinicians can more accurately monitor patients and guide the use of new therapies, such as monoclonal antibodies.

In this regard, it is increasingly being recognized that the end point of severity scoring can be more than just a score representing the degree of physiologic disturbance. Severity scoring can be used, in conjunction with other risk factors (*eg*, disease etiology or patient selection criteria), to anticipate and evaluate outcomes, such as hospital mortality.[37] These probability estimates can be calculated at the time a patient presents for care or for entry into a clinical trial; thus, they can serve as a pretreatment control. They can also be updated during the course of therapy, thereby describing the course of illness and providing an alternative for the evaluation of response. The methods for calculating these dynamic probability estimates are not as developed, however, as are those for initial

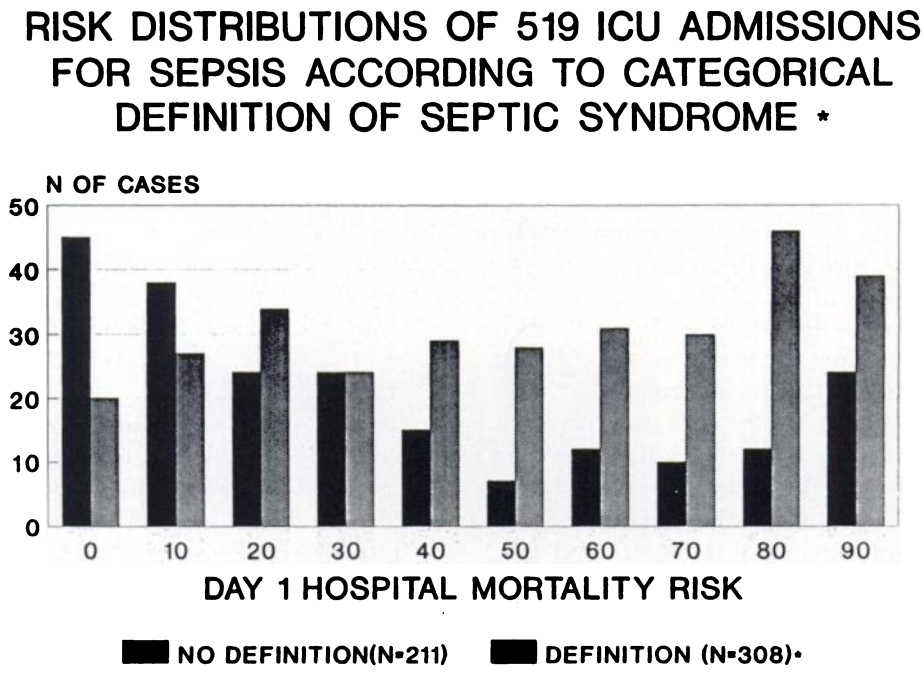

Figure 3. Risk distribution of 519 sepsis patients who either met (n = 308) or did not meet (n = 211) the criteria for sepsis syndrome (see reference 40 for further details).

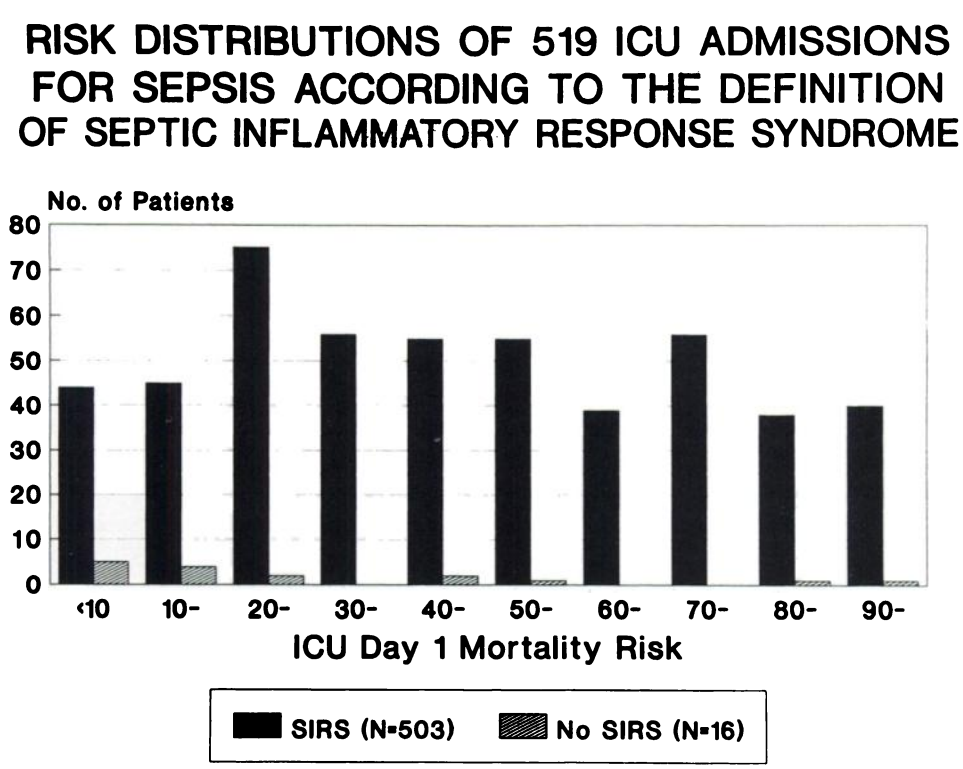

FIGURE 4. Risk distribution of the same 519 sepsis patients as in Figure 3, according to whether they met criteria for SIRS.

or presentation risk assessment.[39]

To illustrate the value of combining initial severity scoring or probability risk estimation with the newly proposed definition for SIRS, the study group reviewed the application of hospital mortality risk estimation to a group of 519 adult patients with a primary diagnosis of sepsis upon admission to medical and surgical ICU.[40] These patients frequently lacked an initial microbial source of infection, such as bacterial pneumonia, but were still identified and treated as suffering primarily from infection. As such, they represent a subgroup of patients with sepsis for whom the new definitions, such as SIRS, would be appropriate (Fig 1).

Figure 3 illustrates the distribution of hospital mortality risk calculated on the initial day of ICU treatment for these 519 patients, according to whether the patient met criteria for the definition of sepsis syndrome, as defined by Bone et al.[11] It can be seen that the risk distribution of the 308 (59 percent) patients meeting the criteria for this syndrome is not substantially different from that for the 211 (41 percent) patients who did not fulfill the criteria.

In contrast, the result depicted in Figure 4 illustrates that when the SIRS definition was applied to the same 519 patients with a primary clinical diagnosis of sepsis, it identified 96.9 percent (503/519). What this initial application of the new definition has achieved, therefore, is an increase in the number of patients classified by the definition. This is important, since the previous definition (sepsis syndrome) excluded many of these patients, although their estimated risks were equivalent to those of patients who were included.[40]

Finally, Figure 5 demonstrates that, for the 503 patients meeting the criteria for SIRS, the estimated mortality risks calculated on the initial day of ICU treatment accurately predicted the subsequent actual hospital mortality rates. This demonstrates the current capability of severity scoring and risk estimation when used in combination with a broad, encompassing clinical definition like SIRS. Further details on these methods are available[39,40] and will be the subject of a subsequent report from this consensus conference. These findings led to the following recommendations.

Recommendation 1

Because of the increasing complexity of patient presentation, the use of new terminology, such as SIRS, with its various etiologies (Fig 1) should be combined with risk stratification or probability risk estimation techniques in order to measure the position of an individual patient along the continuum of severity.

Rationale: The major change in patient presentation has been an increase in the complexity of illness. Also, more severely ill patients are being treated at later stages of their illness. Accurate identification of pretreatment risk can improve the precision of the evaluation of new therapies. Such risk estimation can also

be useful in monitoring the utilization of new therapies and in refining the indications for specific treatments by identifying risk levels when certain therapies appear to be efficacious. The use of this approach is particularly important when the patient is a candidate for, or a participant in, a clinical trial.

Recommendation 2

When patients are identified as having SIRS or MODS, sequential (daily or more frequently) risk stratification or probability estimation techniques should be applied to describe the course of these syndromes.

Rationale: At our current level of understanding (and measurement capabilities), we determine the course of SIRS by relying primarily on sequential measurements of physiologic changes. These physiologic changes correlate with subsequent outcome. In the future, it may be possible to extend this measurement to include metabolic changes.[41] Such advances in measurement capabilities may be especially important in characterizing the course of MODS. As emphasized previously, the exact criteria for, and description of, MODS have yet to be determined.

Recommendation 3

Priority should be given to building on severity scoring and other predictive and descriptive efforts. This will allow the development of a comprehensive model of disease progression that will have implications for the investigation of new syndromes such as SIRS and MODS.

Rationale: The development of a comprehensive model for a syndrome, such as SIRS, is a complex process. Such a model must describe the pre-ICU treatment interval with respect to time and therapy and the changes in physiologic and metabolic parameters over time, while remaining unaffected by variations in practice styles. Ideally, the variables involved would be independent, would distinguish control or disease-initiating effects from response effects, and would be path-independent for an individual patient.

Conclusion

While examples of such model systems exist,[42,43] a number of significant problems remain. We are currently unable to determine which physiologic, clinical, or metabolic variables cause, and which are caused by, the inflammatory response. We have difficulty labeling and then reliably identifying diseases. We also know that the measurement of a number of variables currently in use, such as the level of oxygen consumption or the cardiac output, may vary with practice style. Very large data bases are also necessary to establish whether any reduced or streamlined data set retains its validity. Despite these and other substantial obstacles, it is becoming apparent that a small number of variables can accurately capture most of the mean-

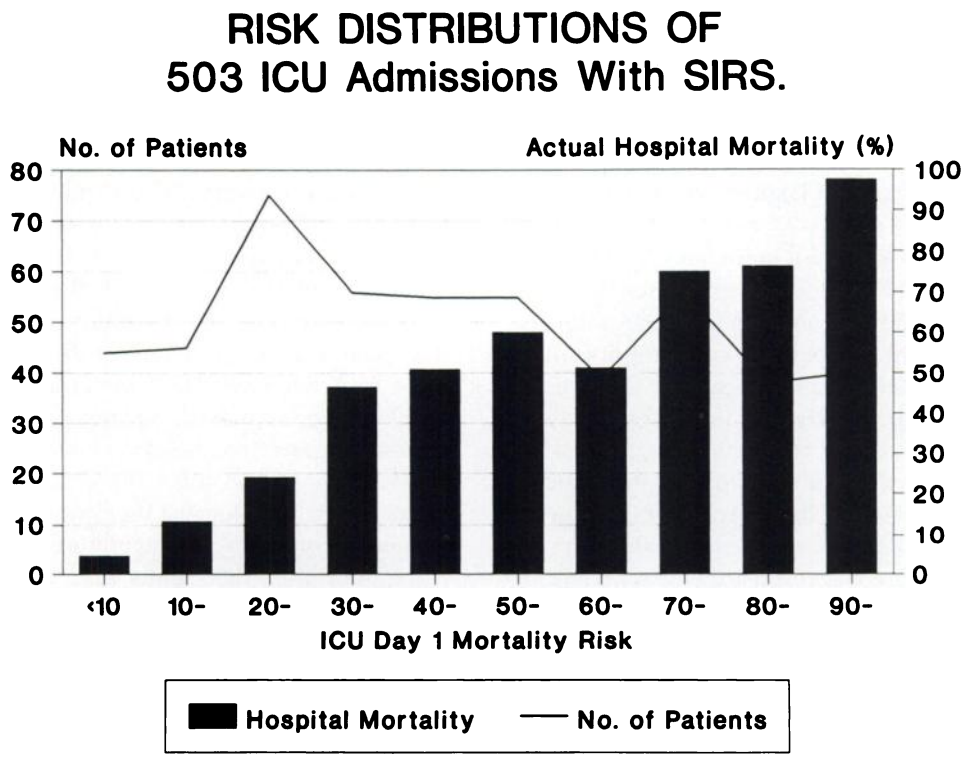

FIGURE 5. Risk distribution of 503 septic patients who met the criteria for SIRS. This demonstrates the relationship between risk of hospital mortality, calculated on the first day of the ICU stay, and actual hospital mortality rates.

ingful data defining physiologic response currently present in large data sets. This provides encouragement that, while the ideal model for describing the response of patients with complex illnesses, such as SIRS, does not currently exist, it is a goal worth attempting to achieve.

Guidelines for the Use of Innovative Therapies in Severe Sepsis

Innovative therapy in severe sepsis usually involves an attempt to alter the systemic inflammatory response of a patient. Such forms of therapy are quite different from supportive therapy or therapies that are directed at the causative organism (*eg*, antibiotics or surgical procedures). Despite the use of these current therapies, the morbidity and mortality rates in severe sepsis remain high. Over the last 10 to 15 years, new antibiotics and increasingly sophisticated critical care have had little impact on the mortality rate of this disease.

A variety of innovative therapies aimed at the mediators of inflammation have recently undergone clinical trials, and this line of investigation is likely to continue. To recruit appropriate numbers of patients who meet the entry criteria for the various studies and to gain significant statistical power, multicenter trials are usually necessary. The results of these trials should be used as a guide to the rational use of new therapies that are developed.

Multicenter clinical trials and product development are very expensive. This will impose significantly increased costs on the product being investigated if it becomes clinically available. The majority of these innovative therapies will, therefore, entail significant expenses for the health care consumer, although their impact on the total cost of health care remains to be determined.

There are well-established guidelines for conducting clinical tests,[44,45] including adherence to good clinical practice and the protection of human subjects. These guidelines are particularly important in clinical trials that investigate the causes of sepsis. The issue of language was a central focus of this conference, and we recommend the use of the terminology discussed earlier in this report in conjunction with that used in published peer-reviewed clinical trials.[7-10] The use of established terminology may make it possible to more competently compare the results of efficacy trials for innovative agents in the treatment of sepsis. The comparison of trials would also be facilitated by standardized trial design, data collection, and reporting of data. Further, it may be anticipated that problems with terminology will only get worse as additional agents are tested, either alone or in combination.

The choice of patients for entry into trials should be as selective as possible, particularly when the trial targets a subgroup of the septic population (*eg*, patients with Gram-negative sepsis). Patients whose underlying disease is not likely to permit them to survive the study should be excluded, as should those who are not candidates for aggressive medical therapy. As our ability to define specific subgroups improves, the entry criteria to future trials should reflect these changes.

The design of trials in sepsis research should entail well-defined end points, including the reporting of deaths from any cause, through a minimum of 28 days after study enrollment. Overall hospital mortality, as well as the resolution of organ dysfunction, should also be reported. We encourage researchers to report data relevant to the cost of therapy and quality of life. The analysis of adverse outcomes in the overall group, as well as in the treatment group or any other group of interest, should be presented. The reporting of results should include a detailed analysis that demonstrates the comparability of noninvestigational treatments and patient characteristics among groups. It is important to address potential predictors of clinical outcome, such as underlying disease and the referral source of the patients, and to ensure that they are treated adequately in the statistical analysis of the data. Severity-of-illness scoring systems should be used in the stratification of patient risk to the extent that the individual scoring system has been independently demonstrated to predict outcome in septic patients. The interval between fulfillment of entry criteria and administration of experimental intervention, as well as other indicators of possible lead time bias, should be noted and analyzed.

In the approved use of new therapies for treating sepsis, the selection of suitable patients to receive these innovative treatments is an important consideration for the clinician. The expected impact of the treatment on the disease process of the patient should be considered; the prospective identification of patients for whom the treatment would be most efficacious is important. The morbidity and mortality rates that would have occurred in the absence of the innovative therapy and the safety profile of the product should also be appraised. A patient who is to be treated with an innovative therapy should have a clinical presentation that matches the entrance criteria used in the clinical trial for that therapy. However, for some entrance criteria (*ie*, temperature, heart rate, and respiratory rate), rigid limits were set for the purpose of conducting a clinical trial. When objective data have allowed a definitive diagnosis of the target population for which the innovative therapy is intended, exceptions to the listed entrance criteria can be made. For example, in considering a therapy that utilizes antibodies raised against endotoxin for a patient who has a positive blood culture for Gram-negative bacteria, tachypnea, tachycardia, and hypotension, the failure

to meet temperature criteria from a previous clinical trial should not be used as a reason to withhold treatment. Also, since the Food and Drug Administration has access to a larger data base on any given agent, FDA labeling indicators may be different from clinical trial entrance criteria, and may thus preempt them.

Patients for whom exclusion criteria might be overlooked include those who are younger than 18 years old, those who are pregnant, and those with uncontrolled hemorrhage. Such patients are frequently excluded from clinical trials as a matter of protocol, not because of any anticipated risk to efficacy. For these excluded populations, treatment may offer a significant benefit. The individual physician must assess the risks or benefits of therapy for each patient. Patients with burns, neutropenia, and transplanted organs may also be excluded from clinical trials due to the potentially disparate effects of therapy. If innovative therapy is found to be beneficial in nonexcluded groups, then additional clinical trials may be appropriate for certain excluded groups, such as the three groups mentioned above. In the interim, potential risks and unproven benefits should be considered prior to any decision to institute therapy. Finally, patients who are receiving less than full support are frequently not included in clinical trials. A decision to treat such patients must be made with ethical and cost-containment considerations in mind; it must be remembered that the efficacy of treatment in this group is unknown.

For those therapies that are directed at bacterial infections or the products of bacteria, such as endotoxin, it is important to obtain information about the specific etiologic agent so that the appropriate treatment method can be used. The utilization of previous culture results and current Gram stains of specimens from suspected sites of infection are imperative for good decision making. For example, a patient with Gram stain evidence of *Staphylococcus* as the probable infecting agent is not likely to benefit from the utilization of antiendotoxin antibodies.

These innovative therapies are typically characterized as having a potentially important influence on patient outcome, a substantial impact on health care costs, and a restrictive set of indications for use. These characteristics necessitate an increased responsibility on the part of the corporations developing and marketing the therapy to provide scientifically appropriate assistance and education to the clinicians or institutions who must determine how and when to use it. This information should be helpful in the selection of individuals who could potentially benefit from the therapy. This responsibility may also necessitate additional studies or documentation in the future to meet changing requirements for the formal approval of the therapy.

In the absence of published data supporting alterations in the frequency or amount of an agent that should be administered in innovative therapy, physicians should dose precisely as was done in the methodology of the clinical trial that showed efficacy. Unless supported by published literature, the effect of innovative therapy in the treatment of recurrent sepsis cannot be predicted. However, in those patients suspected of having accelerated drug clearance, as in cases of plasmapheresis and massive bleeding, redosing may be considered, although there are no available data on what effect, if any, these conditions have on the bioavailability of the agent or on its therapeutic effect.

Most innovative therapies will be expensive and intended only for specific populations of patients. These populations will be identified through the results of clinical trials. Overutilization is an important issue, particularly if the identification of the target population is difficult and there is no anticipated toxicity. Equally important is the assurance that there will not be underutilization of the innovative therapy in patient groups that would be likely to benefit. Methods of ensuring proper patient selection will vary, based on the character of the particular medical institution. Each hospital must consider its own situation and devise appropriate methods to ensure that the proper innovative therapy for sepsis is employed.

Potential mechanisms for accomplishing this goal include the placement of physicians with expertise in the diagnoses of the particular disorders to be treated in a position to guide the utilization of innovative therapies. An approval process involving these physicians may be warranted. These physicians should be readily available, so that treatment with innovative therapy is not delayed; on-site expertise is preferable to off-site expertise. When a specially trained physician is not available, the use of patient selection criteria checklists to assist the prescribing physician may be helpful. The checklists may also be useful for other situations in which the initial contact physician is not an expert in sepsis and innovative therapy.

With the input of physicians and pharmacists, systems should be designed and implemented prospectively as a quality assurance mechanism to evaluate the utilization of innovative therapy. Patient selection checklists may help prevent overutilization; monitoring for underutilization is more difficult. It is especially important for individual physicians to exercise caution in the use of potentially deleterious therapies.

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Gordon R. Bernard, M.D., F.C.C.P., Associate Professor of Medicine, Vanderbilt University Medical School, Nashville
James W. Biondi, M.D., Pulmonary and Critical Care Section, Yale University School of Medicine, New Haven
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William W. Merrill, M.D., Chief, Pulmonary Section, West Haven VA Medical Center, West Haven, Conn
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Herbert P. Wiedemann, M.D., Chairman, Department of Pulmonary and Critical Care Medicine, Cleveland Clinic Foundation, Cleveland
Cornelius H. Wortel, M.D., Adjunct Clinical Assistant Professor of Medicine, Critical Care/Emergency Medicine Section, Department of Medicine, Ben Taub General Hospital, Houston

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