2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Mitchell M. Levy, MD, FCCP; Mitchell P. Fink, MD, FCCP; John C. Marshall, MD; Edward Abraham, MD; Derek Angus, MD, MPH, FCCP; Deborah Cook, MD, FCCP; Jonathan Cohen, MD; Steven M. Opal, MD; Jean-Louis Vincent, MD, FCCP, PhD; Graham Ramsay, MD; For the International Sepsis Definitions Conference

Objective: In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a “Consensus Conference,” the goals of which were “to provide a conceptual and a practical framework to define the systemic inflammatory response to infection, which is a progressive injurious process that falls under the generalized term ‘sepsis’ and includes sepsis-associated organ dysfunction as well.” The general definitions introduced as a result of that conference have been widely used in practice and have served as the foundation for inclusion criteria for sepsis-associated organ dysfunction as well. “The general definitions introduced as a result of that conference have been widely used in practice and have served as the foundation for inclusion criteria for sepsis-associated organ dysfunction as well.” The general definitions introduced as a result of that conference have been widely used in practice and have served as the foundation for inclusion criteria for sepsis-associated organ dysfunction as well. “The general definitions introduced as a result of that conference have been widely used in practice and have served as the foundation for inclusion criteria for sepsis-associated organ dysfunction as well.” The general definitions introduced as a result of that conference have been widely used in practice and have served as the foundation for inclusion criteria for sepsis-associated organ dysfunction as well.” The general definitions introduced as a result of that conference have been widely used in practice and have served as the foundation for inclusion criteria for sepsis-associated organ dysfunction as well.”

Design: Several North American and European intensive care societies agreed to revisit the definitions for sepsis and related conditions. This conference was sponsored by the SCCM, The European Society of Intensive Care Medicine (ESICM), The American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS).

Methods: The conference was attended by 29 participants from Europe and North America. In advance of the conference, five subgroups were formed to evaluate the following areas: signs and symptoms of sepsis, cell markers, cytokines, microbiologic data, and coagulation parameters. The subgroups corresponded electronically before the conference and met in person during the conference. A spokesperson for each group presented the deliberation of each group to all conference participants during a plenary session. A writing committee was formed at the conference and developed the current article based on executive summary documents generated by each group and the plenary group presentations. The present article serves as the final report of the 2001 International Sepsis Definitions Conference.

Conclusion: This document reflects a process whereby a group of experts and opinion leaders revisited the 1992 sepsis guidelines and found that apart from expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience, no evidence exists to support a change to the definitions. This lack of evidence serves to underscore the challenge still present in diagnosing sepsis in 2003 for clinicians and researchers and also provides the basis for introducing PIRO as a hypothesis-generating model for future research.

Key Words: sepsis; severe sepsis; septic shock; systemic inflammatory response syndrome; PIRO

In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a “Consensus Conference” in an attempt “to provide a conceptual and a practical framework to define the systemic inflammatory response to infection, which is a progressive injurious process that falls under the generalized term ‘sepsis’ and includes

The 1992 statement from the ACCP/SCCM Consensus Conference introduced into common parlance the Systemic Inflammatory Response Syndrome (SIRS). The acronym provided a reference for the complex findings that result from a systemic activation of the innate immune response, regardless of cause. The statement hypothesized that SIRS is triggered by localized or generalized infection, trauma,
thermal injury, or sterile inflammatory processes, i.e., acute pancreatitis. SIRS is
considered to be present when patients have more than one of the following clini-
cal findings: body temperature, >38°C or <36°C; heart rate, >90 min⁻¹; hyperven-
tilation evidenced by a respiratory rate of >20 min⁻¹ or a PaCO₂ of <32 mm Hg; and
a white blood cell count of >12,000 cells μL⁻¹ or <4,000 μL⁻¹.

The SIRS concept has been globally adopted by clinicians and investigators. A MEDLINE
search dated January 1992–May 2002 yielded almost 800 publications that
mention SIRS in the title or the abstract. We did not record all MEDLINE terms used
to identify all citations relevant to SIRS. Our goal was not to conduct a systematic
review of the literature, which does dictate the need to record the search strategy.

Bone et al. defined sepsis as SIRS plus infection, “severe sepsis” as sepsis associ-
ated with organ dysfunction, hypoperfu-
sion, or hypotension, and “septic shock” as sepsis with arterial hypotension, de-
spite adequate fluid resuscitation. These
general definitions are now widely used
in practice and serve as the basis for nu-
merous clinical trial inclusion criteria.
Recent trial data relating to a number of
new interventions have created a need to
revisit and modify the 1992 definitions to
better reflect our understanding of the
pathophysiology of these syndromes (2,
3). In addition, many clinicians believe
that the 1992 consensus definition does
not provide a clear definition of sepsis. A
recent European Society of Intensive
Care Medicine (ESICM)/SCCM physician
attitudinal survey revealed that 71% of
respondees cited no common definition
of sepsis (4), despite the ACCP/SCCM
consensus conference criteria for sepsis,
severe sepsis, and septic shock (1).

This gap in clinician understanding
and a concurrent increase in critical trial
data provided the support needed for a
review of the 1992 definitions of sepsis
and related conditions. The 2001 Interna-
tional Sepsis Definitions Conference
was sponsored by the SCCM, ESICM, ACCP,
American Thoracic Society, and the Sur-
gical Infection Society. Each of the spon-
sors provided official representation at
the conference and during the prepara-
tion of this article.

Goals and Methods of
Conference

The overall goals of the conference
were threefold and began with a view of
the strengths and weaknesses of the cur-
rent definitions of sepsis and related con-
ditions. The second goal focused on the
identification of ways to improve the cur-
rent definitions. The final goal sought to
identify methodologies for increasing the
accuracy, reliability, and/or clinical util-
ity of the diagnosis of sepsis.

The conference was held in Washing-
ton, DC, in December 2001 and included
29 participants from Europe, North
America, and the United Kingdom. Before
convening, five subgroups were formed
to evaluate the signs and symptoms of
sepsis, cell markers, cytokines, microbio-
logic data, and coagulation parameters.
Subgroup participants corresponded
electronically before meeting in person at
the conference. A subgroup spokesperson
presented individual deliberations to all
conference participants during plenary
sessions. A writing committee, formed at
the conference, developed this article
based on subgroup executive summary
documents and the plenary sessions. Ad-
nitional information was introduced for
participant review after the conference
during telephone, E-mail, and live discus-
sions. This article serves as the final re-
port of the 2001 International Sepsis De-
finitions Conference.

Definitions

Establishing working definitions for a
syndrome is inherently an imperfect pro-
cess and one that requires periodic up-
dating on the basis of new insights into
pathophysiology or the availability of new
diagnostic tests. We point to the example
of acute myocardial infarction (AMI) as a
disease paradigm to illustrate this point.
Generally accepted diagnostic criteria for
AMI were formulated by the Joint Inter-
national Society and Federation of Cardi-
ology/World Health Organization task
force in 1979 (5). Although AMI is easily
diagnosed when Q-waves are present on
the electrocardiogram, non-Q-wave AMI
can be distinguished from unstable an-
gina pectoris only by using biochemical
markers. Reflecting the contemporary
state of knowledge, the World Health Or-
ganization biochemical criterion for es-
tablishing the diagnosis of AMI was a
total creatine kinase concentration
greater than twice the upper limit of nor-
mal (5). Subsequently, several more sen-
sitive and specific biochemical markers of
myocardial cell death were introduced
into clinical practice (6–8), and as a re-
sult, the diagnostic criteria for AMI have
been revised (9).

Unfortunately, a clinically useful set of
criteria for diagnosing sepsis and related
conditions will necessarily be somewhat
arbitrary. There is no “gold standard”
(such as the infarcted myocardium) against
which the diagnostic criteria can be
calibrated. Diagnostic criteria will be
judged successful if clinicians regard
them as an aid for decision-making at the
bedside. The diagnostic scheme requires
sufficient sensitivity and specificity to be
a clinical aid.

SIRS

The SIRS concept is valid to the extent
that a systemic inflammatory response
can be triggered by a variety of infectious
and noninfectious conditions. Signs of
systemic inflammation can and do occur
in the absence of infection among pa-
tients with burns, pancreatitis, and other
disease states. However, the specific cri-
teria proposed in the 1992 consensus de-
finitions are widely considered to be too
nonspecific to be of utility in diagnosing a
cause for the syndrome or in identifying a
distinct pattern of host response (2, 3).

Although the clinical manifestations
of systemic inflammation are protean,
the biochemical features may be more
consistent. Investigators have detected
elevated circulating levels of interleukin
(IL)-6 (10), adrenomedullin (11), soluble
(s)CD14, sELAM-1, MIP-1α (12), extracel-
lar phospholipase A₂ (13), and C-reac-
tive protein (14) in patients meeting the
1992 SIRS criteria. In the future, if sup-
ported by further epidemiologic data, it
may be possible to use purely biochemi-
cal and/or immunologic, rather than
clinical, criteria to identify the inflamma-
tory response. It may be that inflamma-
tion is present when the circulating con-
centration of IL-6, procalcitonin (15–17),
or C-reactive protein are increased. No
large prospective studies currently sup-
port such a conclusion.

Sepsis

In contrast to SIRS, it is very impor-
tant that clinicians and researchers have
the tools needed to recognize and diag-
nose sepsis promptly; effective therapies
for infection are widely and readily avail-
able. As in 1992, we define sepsis to be
the clinical syndrome defined by the presence
of both infection and a systemic inflam-
matory response. In considering whether
the diagnostic criteria for infection or systemic inflammation should be revised, we adhere to several principles. The criteria should be broadly useful both to clinicians caring for patients at the bedside and to researchers designing observational studies and clinical trials to improve the understanding of sepsis and its optimal treatment. The criteria should be sensitive enough to identify most patients with the syndrome, while minimally sacrificing inevitable specificity. The criteria should not be so cumbersome that clinicians will resist a commitment to memory or application. Any laboratory-dependent criteria should use assays that either are widely available now or are likely to be generally available in the near future. The criteria should be applicable to adult, pediatric, and neonatal patients. Infection. We defined infection as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms. This definition, essentially the same one used in the 1992 document, is not perfect. For example, colitis caused by Clostridium difficile, results from overgrowth of this organism in the colon, which is certainly not sterile. Furthermore, the clinical manifestations of C. difficile colitis are not caused by the bacteria invading normally sterile tissues but, rather, by the cytopathic effects of an exotoxin secreted by the organism. It is also important to point out that, frequently, infection is strongly suspected without being microbiologically confirmed. Accordingly, sepsis (i.e., infection and the systemic response to it) may only be strongly suspected, without being microbiologically confirmed.

**Systemic Inflammation in Response to Infection.** Because of the limitations of SIRS discussed above, we included a list of possible signs of systemic inflammation in response to infection (Table 1). Ultimately, this scheme seeks to codify the physical and laboratory findings that prompt an experienced clinician to conclude that an infected patient “looks septic.” Findings indicative of early organ dysfunction may be the first symptoms noted by clinicians when making this assessment. It is for this reason that we included findings such as hemodynamic instability, arterial hypoxemia, oliguria, coagulopathy and altered liver function tests among the list of criteria that can be used to establish the diagnosis of sepsis.

It is important to emphasize that none of the findings in Table 1 is specific for sepsis. A high cardiac output is commonly observed following major surgical procedures or multiple trauma. Arterial hypotension can be caused by many conditions other than sepsis, such as acute left ventricular failure secondary to AMI or hemorrhage. Coagulopathy can be drug-induced and is associated with many different diseases, in addition to sepsis. It is important that as a practitioner “checks off the boxes” to establish the diagnosis of sepsis, only findings that cannot be easily explained by other causes be included. The thresholds chosen in Table 1 merit discussion. We have not chosen thresholds for each of the criteria that are consistently abnormal in degree. The proposition is whether thresholds similar in degree of abnormality confer similar prediction in sepsis.

As a result, the group turned toward the day-to-day “reality” for bedside clinicians. Group consensus concluded that few, if any, patients in the early stages of the inflammatory response to infection are diagnosed with sepsis via four arbitrary criteria. Instead, the clinician goes to the bedside, identifies myriad symptoms, and regardless of an evident infection, declares the patient to “look septic.” If no obvious source of infection exists, the clinician then initiates a search for an infectious origin of the signs and symptoms associated with sepsis. The use of the word “some” reflects the clinical reality at the bedside, rather than an arbitrary list invented for the purpose of clinical trial entry criteria. Should the definition of sepsis reflect reality as seen at the bedside, thereby facilitating a clinical diagnosis, or should the definition enable investigators to develop clear and simple entry criteria for clinical trials? It was the opinion of the group that facilitating a bedside diagnosis should have primacy over research entry criteria.

### Table 1. Diagnostic criteria for sepsis

<table>
<thead>
<tr>
<th>General variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (core temperature &gt;38.3°C)</td>
</tr>
<tr>
<td>Hypothermia (core temperature &lt;36°C)</td>
</tr>
<tr>
<td>Heart rate &gt;90 min⁻¹ or &gt;2 SD above the normal value for age</td>
</tr>
<tr>
<td>Tachypnea</td>
</tr>
<tr>
<td>Altered mental status</td>
</tr>
<tr>
<td>Significant edema or positive fluid balance (&gt;20 mL/kg over 24 hrs)</td>
</tr>
<tr>
<td>Hyperglycemia (plasma glucose &gt;120 mg/dL or 7.7 mmol/L) in the absence of diabetes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytosis (WBC count &gt;12,000 µL⁻¹)</td>
</tr>
<tr>
<td>Leukopenia (WBC count &lt;4000 µL⁻¹)</td>
</tr>
<tr>
<td>Normal WBC count with &gt;10% immature forms</td>
</tr>
<tr>
<td>Plasma C-reactive protein &gt;2 SD above the normal value</td>
</tr>
<tr>
<td>Plasma procalcitonin &gt;2 SD above the normal value</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamic variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypotension (SBP &lt;90 mm Hg, MAP &lt;70, or an SBP decrease &gt;40 mm Hg in adults or &lt;2 SD below normal for age)</td>
</tr>
<tr>
<td>SvO₂ &gt;70%</td>
</tr>
<tr>
<td>Cardiac index &gt;3.5 L/min⁻¹-M⁻²³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ dysfunction variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypoxemia (PaO₂/FiO₂ &lt;300)</td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt;0.5 mL·kg⁻¹·hr⁻¹ or 45 mmol/L for at least 2 hrs)</td>
</tr>
<tr>
<td>Creatinine increase &gt;0.5 mg/dL</td>
</tr>
<tr>
<td>Coagulation abnormalities (INR &gt;1.5 or aPTT &gt;60 secs)</td>
</tr>
<tr>
<td>Ileus (absent bowel sounds)</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt;100,000 µL⁻¹)</td>
</tr>
<tr>
<td>Hyperbilirubinemia (plasma total bilirubin &gt;4 mg/dL or 70 mmol/L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue perfusion variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlactatemia (&gt;1 mmol/L)</td>
</tr>
<tr>
<td>Decreased capillary refill or mottling</td>
</tr>
</tbody>
</table>

WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; SvO₂, mixed venous oxygen saturation; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

“Infection defined as a pathologic process induced by a microorganism; aSvO₂ sat >70% is normal in children (normally, 75–80%), and CI 3.5–5.5 is normal in children; therefore, NEITHER should be used as signs of sepsis in newborns or children; “diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5 or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.
Severe Sepsis (Sepsis with Organ Dysfunction)

The definition of severe sepsis remains unchanged and refers to sepsis complicated by organ dysfunction. Severe sepsis is now considered to be the most common cause of death in noncoronary critical care units. Approximately 150,000 people die annually in Europe and >200,000 die annually in the United States (18). Organ dysfunction can be defined using the definitions developed by Marshall et al. (19) or the definitions used for the Sequential Organ Failure Assessment (SOFA) score (20). Organ dysfunction in severe sepsis in the pediatric population can be defined using definitions developed by Wilkinson et al. (21), Proulx et al. (22), and Doughty et al. (23) or the definitions used for the PEMOD and PELOD score (24).

Septic Shock

Septic shock in adults refers to a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Hypotension is defined by a systolic arterial pressure below 90 mm Hg (or, in children, <2 SD below normal for their age), a MAP <60, or a reduction in systolic blood pressure of >40 mm Hg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension. Children and neonates maintain higher vascular tone than adults. Therefore, the shock state occurs long before hypotension in children. Septic shock in pediatric patients is defined as a tachycardia (may be absent in the hypothermic patient) with signs of decreased perfusion including decreased peripheral pulses compared with central pulses, altered alertness, flush capillary refill or capillary refill >2 secs, mottled or cool extremities, or decreased urine output (25). Hypotension is a sign of late and decompen-sated shock in children.

Developing a Staging System for Sepsis

Despite the definitions for sepsis, severe sepsis, and septic shock outlined above, these terms do not allow for precise characterization and staging of patients with this condition. A clinically useful staging system stratifies patients with a disease by both their baseline risk of an adverse outcome and their potential to respond to therapy. Such systems, both formal and informal, are widely used in clinical medicine. Perhaps the best-developed and most explicit approach to disease stratification has evolved in oncology. The TNM system, developed by Pierre Denoix in 1946 (26), classifies malignant tumors based on descriptors for the primary tumor itself (T), metastases to regional lymph nodes (N), and distant metastases (M). Each domain is graded to denote the extent of pathologic involvement. For any given tumor type, survival tends to correlate with certain TNM subgroups.

Using a variation of the TNM approach, we developed a classification scheme for sepsis—called PIRO—that will stratify patients on the basis of their predisposing conditions, the nature and extent of the insult (in the case of sepsis, Infection), the nature and magnitude of the host Response, and the degree of concomitant organ dysfunction (Table 2). It is important to emphasize that the PIRO concept is rudimentary; extensive testing and further refinement will be needed before it can be considered ready for routine application in clinical practice.

Predisposition. Premorbid factors have a substantial impact on outcome in sepsis, modifying both the disease process and the approach taken to therapy. This point is emphasized by recent data showing that genetic factors play a greater role in determining the risk of premature mortality due to sepsis than they do in influencing the risk of premature death from other common conditions, such as cancer or cardiovascular diseases (27). Beyond genetic variability, however, the management of patients with sepsis, and hence the outcome of the disease, is clearly influenced by factors

Table 2. The PIRO system for staging sepsis

<table>
<thead>
<tr>
<th>Domain</th>
<th>Present</th>
<th>Future</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposition</td>
<td>Premorbid illness with reduced probability of short term survival. Cultural or religious beliefs, age, sex.</td>
<td>Genetic polymorphisms in components of inflammatory response (e.g., TLR, TNF, IL-1, CD14); enhanced understanding of specific interactions between pathogens and host diseases.</td>
<td>In the present, premorbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult heavily dependent on genetic predisposition (future). Specific therapies directed against inciting insult require demonstration and characterization of that insult.</td>
</tr>
<tr>
<td>Insult infection</td>
<td>Culture and sensitivity of infecting pathogens; detection of disease amenable to source control.</td>
<td>Assay of microbial products (LPS, mannan, bacterial DNA); gene transcript profiles.</td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>SIRS, other signs of sepsis, shock, CRP.</td>
<td>Non-specific markers of activated inflammation (e.g., PCT or IL-6) or impaired host responsiveness (e.g., HLA-DR); specific detection of target of therapy (e.g., protein C, TNF, PAF).</td>
<td>Both mortality risk and potential to respond to therapy vary with non-specific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator. Response to preemptive therapy (e.g., targeting microorganism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present.</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Organ dysfunction as number of failing organs or composite score (e.g., MODS, SOFA, LODS, PEMOD, PELOD).</td>
<td>Dynamic measures of cellular response to insult—apoptosis, cytopathic hypoxia, cell stress.</td>
<td></td>
</tr>
</tbody>
</table>

TLR, Toll-like receptor; TNF, tumor necrosis factor; IL, interleukin; LPS, lipopolysaccharide; SIRS, systemic inflammatory response syndrome; CRP, C-reactive protein; PCT, procalcitonin; HLA-DR, human leukocyte antigen-DR; PAF, platelet-activating factor; MODS, multiple organ dysfunction syndrome; SOFA, sepsis-related organ failure assessment; LODS, logistic organ dysfunction system; PEMOD, pediatric multiple organ dysfunction; PELOD, pediatric logistic organ dysfunction.
such as the premorbid health status of the patient, the reversibility of concomitant diseases, and a host of religious and cultural forces that shape the approach toward therapy. It is also important to appreciate that these multiple predisposing factors could influence both the incidence and the outcome in similar or conflicting ways. They could also pose separate or different risks for each of the different stages of infection, response, and organ dysfunction. For example, immunosuppression may increase a person’s risk of infection, decrease the magnitude of that person’s inflammatory response, and have no direct influence on organ dysfunction. Similarly, a genetic polymorphism such as the TNF2 allele may result in a more aggressive inflammatory response to an invading organism. This might decrease a person’s risk of infection but increase that person’s risk of an overly exuberant, and potentially harmful, inflammatory response should that patient become infected. We encourage researchers to explore further the complex interaction of the multiple factors that predispose to the onset, stages of progression, and outcome of sepsis.

**Infection.** The site, type, and extent of the infection have a significant impact on prognosis. A bilateral bronchopneumonia is a more extensive process than a localized pneumonia, and a generalized fecal peritonitis is a more extensive process than an appendicitis. By studying mortality rates among patients randomized to receive placebo in recent randomized clinical trials of new agents for the adjuvant treatment of sepsis, it is apparent that pneumonia and intra-abdominal infections are associated with a higher risk of mortality than are urinary tract infections. Patients with secondary nosocomial bacteremia experience a higher mortality than those with catheter-related or primary bacteremia (28). Similarly, there is evidence that the endogenous host response to Gram-positive organisms differs from that evoked by Gram-negative organisms (29). Early studies with antibodies directed against endotoxin, for example, suggested that benefit was greatest in patients with Gram-negative infection (30) or endotoxemia (31) but that treatment might be harmful to patients with Gram-positive infection (32).

**Response.** In general, current therapies for sepsis target the host response, rather than the infecting organism. The host response has proven to be difficult to characterize. Putative biologic markers of response severity include circulating levels of procalcitonin (16, 33), IL-6 (34, 35), and many others. When a new mediator is identified, epidemiologic studies will be required to determine whether measurements of the compound can be useful for staging patients. Furthermore, the optimal set of biologic markers for staging sepsis may depend on the nature of the therapeutic decision to be made. For example, an indicator of dysregulation of the coagulation system might be more valuable for making a decision about whether to institute therapy with drotrecogin alfa (activated) (36), whereas a marker of adrenal dysfunction might be more useful for determining whether to institute therapy with hydrocortisone (37).

**Organ Dysfunction.** By analogy with the TNM system, the presence of organ dysfunction in sepsis is similar to the presence of metastatic disease in cancer. Certainly, the severity of organ dysfunction is an important determinant of prognosis in sepsis (19, 38). Whether the severity of organ dysfunction can aid in therapeutic stratification is less clear. Nevertheless, there is some evidence that neutralization of TNF, an early mediator in the inflammatory cascade, is more effective in patients without significant organ dysfunction (39), whereas drotrecogin alpha (activated) may provide more benefit to patients with greater as compared with lesser disease burden (40). The modern organ failure scores can be used to quantitatively describe the degree of organ dysfunction developing over the course of critical illness (41).

The potential utility of the proposed PIRO model lies in being able to discriminate morbidity arising from infection and morbidity arising from the response to infection. Interventions that modulate the response may impact adversely on the ability to contain an infection; conversely, interventions that target the infection are unlikely to be beneficial if the morbidity impact is being driven by the host response. Premorbid conditions establish a baseline risk, independent of the infectious process, while acquired organ dysfunction is an outcome to be prevented.

The PIRO system is proposed as a template for future investigation and is a work in progress, rather than a model to be adopted. Its elaboration will require extensive evaluation of the natural history of sepsis to define those variables that predict not only an adverse outcome but also the potential to respond to therapy. The parameters selected may well vary depending on the aspect of sepsis being studied, being different, for example, if the focus is the antibiotic treatment of pneumonia, the evaluation of a novel inhibitor of tyrosine kinases, or the optimizing of microcirculatory flow in sepsis. The methodologic challenge is at least as great as that faced by oncologists, and the TNM system continues to evolve more than half a century after its introduction.

**CONCLUSIONS**

The 2001 conference participants convened with the belief that the body of bench work since the 1991 sepsis definitions conference may lead to a major change in the definition of sepsis based on biomarkers. After a process of evidenced-based review and considerable debate, the participants determined that the use of biomarkers for diagnosing sepsis is premature. Given the length and focus of this article, we did not expand on how the problem of defining sepsis has hampered progress. We realize that this issue has long been debated in the medical community, and we choose not to elaborate here.

The primary issue debated was the importance of an accurate diagnosis of sepsis at the bedside when weighed against...
the development of clear and simple entry criteria for clinical trials. Participants believe that the facilitation of bedside diagnosis should have priority over standardized sepsis entry criteria for clinical trials. A standardized set of signs and symptoms that may aid enrollment into randomized trials remains to be developed. Our conclusions can be summarized as follows (Table 3).

1. Current concepts of sepsis, severe sepsis, and septic shock remain useful to clinicians and researchers. Until further evidence arises that justifies altering these categories that describe the host response to infection, they should remain as described 10 yrs ago.

2. These definitions do not allow for precise staging or prognostication of the host response to infection.

3. While SIRS remains a useful concept, the diagnostic criteria for SIRS published in 1992 are overly sensitive and nonspecific.

4. An expanded list of signs and symptoms of sepsis may better reflect the clinical response to infection.

5. The operational definitions of sepsis may be refined and tested in the future as we increase our understanding of the immunologic and biochemical characteristics of these conditions.

6. We hypothesize that improvements in the management of critically ill patients with serious infections may follow the development of a staging system for sepsis that can better characterize the syndrome on the basis of predisposing factors and premorbid conditions, the nature of the underlying infection, the characteristics of the host response, and the extent of the resultant organ dysfunction.

Table 3. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Primary consensus points
- The current concepts of sepsis, severe sepsis, and septic shock seem to be robust definitions and should remain as described 10 yrs ago.
- Current definitions do not allow for precise staging of the host response to infection.
- Signs and symptoms of sepsis are more varied than the initial criteria established in 1991.
- A list of these signs and symptoms, for the diagnosis of sepsis is presented.
- The future lies in developing a staging system that will characterize progression of sepsis. A new system, PIRO, is proposed for characterizing and staging the host response to infection.

The fact that no new definitions for sepsis are introduced in this conference report is noteworthy. This document reflects a process whereby a group of experts revisited the 1992 sepsis consensus definitions and found that apart from expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience, no evidence exists to support any change in the definitions. This lack of evidence serves to underscore the challenge for clinicians and researchers still present in diagnosing sepsis in 2003 and also provides the basis for introducing PIRO as a hypothesis-generating model for future research.

REFERENCES


20. Ferreira FL, Bota DP, Bross A, et al: Serial evaluation of the SOFA score to predict out-

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
come in critically ill patients. JAMA 2002; 286:1754–1758.


