

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 numerous clinical trials of therapeutic interventions. Nevertheless, there has been an impetus from experts in the field to modify these definitions to reflect our current understanding of the pathophysiology of these syndromes.

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. (Crit Care Med 2003; 31:1250–1256)

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

sepsis-associated organ dysfunction as well" (1). Conference participants, under the chairmanship of Roger C. Bone, MD, sought to provide a broad series of definitions that might ultimately improve our collective ability to diagnose, monitor, and treat sepsis. Bone et al. also addressed the need for a formal sepsis research agenda to include the "standardization of research protocols."

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,

From Brown Medical School/Rhode Island Hospital, Medical Intensive Care Unit, Providence, RI (MML); University of Pittsburgh Medical Center, Division of Critical Care Medicine, Pittsburgh, PA (MPF, DA); Toronto General Hospital, Division of Cellular and Molecular Biology, Toronto, Ontario, Canada (JCM); University of Colorado, Health Science Center, Denver, CO (EA); McMaster University/St. Joseph's Hospital, Division of Critical Care Medicine, Ontario, Canada (DC); Division of Investigative Sciences, Imperial College of Medicine, London, UK (JC); Brown Medical School/Memorial Hospital of Rhode Island, Infectious Disease Division, Providence, RI (SMO); Depart-

ment of Intensive Care, Erasme University Hospital, Brussels, Belgium (J-LV); Department of Surgery, University Hospital, Maastricht, The Netherlands (GR).

Conference participants: Mitchell M. Levy, MD, FCCM, FCCP (Co-Chair); Graham Ramsay, MD (Co-Chair); Edward Abraham, MD, FCCM; Derek Angus, MD, FCCP; Robert Balk, MD, FCCP; Gordon Bernard, MD, FCCP; Julian Bion, MD; Joseph Carcillo, MD; Jean M. Carlet, MD; Jonathan Cohen, MD; Deborah Cook, MD, FCCP; Jean-François Dhainaut, MD; Tim Evans, MD, FRCP, FCCP; Mitchell P. Fink, MD, FCCM, FCCP; Donald E. Fry, MD; Herwig Gerlach, MD, PhD; Steve Lowry, MD; Mark A.

Malangoni, MD; John C. Marshall, MD; George Matuschak, MD, FCCP; Steven M. Opal, MD; Joseph E. Parrillo, MD, FCCM, FCCP; Konrad Reinhart, MD; William J. Sibbald, MD, FCCM, FCCP; Charles L. Sprung, MD, JD, FCCM, FCCP; Jean-Louis Vincent, MD, PhD, FCCM, FCCP; Max H. Weil, MD, PhD, FCCM, FCCP.

Address requests for reprints to: Mitchell M. Levy, MD, Rhode Island Hospital, Brown University School of Medicine, 593 Eddy Street, Providence, RI 02903.

Copyright © 2003 by Lippincott Williams & Wilkins

DOI: 10.1097/01.CCM.0000050454.01978.3B

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 clinical findings: body temperature, $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; heart rate, $>90\text{ min}^{-1}$; hyperventilation evidenced by a respiratory rate of $>20\text{ min}^{-1}$ or a Paco_2 of $<32\text{ mm Hg}$; and a white blood cell count of $>12,000\text{ cells } \mu\text{L}^{-1}$ or $<4,000\text{ cells } \mu\text{L}^{-1}$.

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 associated with organ dysfunction, hypoperfusion, or hypotension, and “septic shock” as sepsis with arterial hypotension, despite *adequate* fluid resuscitation. These general definitions are now widely used in practice and serve as the basis for numerous 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 respondents 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 clinical trial data provided the support needed for a review of the 1992 definitions of sepsis and related conditions. The 2001 International Sepsis Definitions Conference was sponsored by the SCCM, ESICM, ACCP, American Thoracic Society, and the Surgical Infection Society. Each of the sponsors provided official representation at the conference and during the preparation 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 current definitions of sepsis and related conditions. The second goal focused on the identification of ways to improve the current definitions. The final goal sought to identify methodologies for increasing the accuracy, reliability, and/or clinical utility of the diagnosis of sepsis.

The conference was held in Washington, 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, microbiologic 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. Additional information was introduced for participant review after the conference during telephone, E-mail, and live discussions. This article serves as the final report of the 2001 International Sepsis Definitions Conference.

Definitions

Establishing working definitions for a syndrome is inherently an imperfect process and one that requires periodic updating 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 International Society and Federation of Cardiology/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 angina pectoris only by using biochemical markers. Reflecting the contemporary state of knowledge, the World Health Organization biochemical criterion for establishing the diagnosis of AMI was a total creatine kinase concentration greater than twice the upper limit of normal (5). Subsequently, several more sensitive 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 patients with burns, pancreatitis, and other disease states. However, the specific criteria proposed in the 1992 consensus definitions 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-1 α (12), extracellular phospholipase A₂ (13), and C-reactive protein (14) in patients meeting the 1992 SIRS criteria. In the future, if supported by further epidemiologic data, it may be possible to use purely biochemical and/or immunologic, rather than clinical, criteria to identify the inflammatory response. It may be that inflammation is present when the circulating concentration of IL-6, procalcitonin (15–17), or C-reactive protein are increased. No large prospective studies currently support such a conclusion.

Sepsis

In contrast to SIRS, it is very important that clinicians and researchers have the tools needed to recognize and diagnose sepsis promptly; effective therapies for infection are widely and readily available. As in 1992, we define sepsis to be the clinical syndrome defined by the presence of both infection and a systemic inflammatory 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

Table 1. Diagnostic criteria for sepsis

Infection, ^a documented or suspected, and some of the following: ^b
General variables
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C)
Heart rate >90 min ⁻¹ or >2 SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count >12,000 μL ⁻¹)
Leukopenia (WBC count <4000 μL ⁻¹)
Normal WBC count with >10% immature forms
Plasma C-reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic variables
Arterial hypotension ^b (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age)
SvO ₂ >70% ^b
Cardiac index >3.5 L·min ⁻¹ ·M ^{-2.3}
Organ dysfunction variables
Arterial hypoxemia (PaO ₂ /FIO ₂ <300)
Acute oliguria (urine output <0.5 mL·kg ⁻¹ ·hr ⁻¹ or 45 mmol/L for at least 2 hrs)
Creatinine increase >0.5 mg/dL
Coagulation abnormalities (INR >1.5 or aPTT >60 secs)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000 μL ⁻¹)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (>1 mmol/L)
Decreased capillary refill or mottling

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.

^aInfection defined as a pathologic process induced by a microorganism; ^bSvO₂ 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; ^cdiagnostic 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.

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 merits 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.

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, flash capillary refill or capillary refill >2 secs, mottled or cool extremities, or decreased urine output (25). Hypotension is a sign of late and decompensated 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

Domain	Present	Future	Rationale
Predisposition	Premorbid illness with reduced probability of short term survival. Cultural or religious beliefs, age, sex.	Genetic polymorphisms in components of inflammatory response (e.g., TIR, TNF, IL-1, CD14); enhanced understanding of specific interactions between pathogens and host diseases.	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).
Insult infection	Culture and sensitivity of infecting pathogens; detection of disease amenable to source control.	Assay of microbial products (LPS, mannan, bacterial DNA); gene transcript profiles.	Specific therapies directed against inciting insult require demonstration and characterization of that insult.
Response	SIRS, other signs of sepsis, shock, CRP.	Nonspecific 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).	Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator.
Organ dysfunction	Organ dysfunction as number of failing organs or composite score (e.g., MODS, SOFA, LODS, PEMOD, PELOD).	Dynamic measures of cellular response to insult—apoptosis, cytopathic hypoxia, cell stress.	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.

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 alfa (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 his-

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.

tory 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

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.

SCCM, Society of Critical Care Medicine; ESICM, European Society of Intensive Care Medicine; ACCP, American College of Chest Physicians; ATS, American Thoracic Society; SIS, Surgical Infection Society; PIRO, stratifies 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.

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.

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

1. Members of the American College of Chest Physicians/Society of Crit Care Med Consensus Conference Committee: American College of Chest Physicians/Society of Crit Care Med Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20:864–874
2. Marshall JC: SIRS and MODS: What is their relevance to the science and practice of intensive care? *Shock* 2000; 14:586–589
3. Vincent J-L: Dear SIRS, I'm sorry to say that I don't like you. *Crit Care Med* 1997; 25: 372–374
4. Ramsay G, Gerlach H, Levy MM, et al: An international sepsis survey: A Study of doctors' knowledge and perception about sepsis. *Crit Care Med* 2003; 31:
5. Nomenclature and Criteria for Diagnosis of Ischemic Heart Disease: Report of the Joint International Society and Federation of Cardiology/World Health Organization Task Force on Standardization of Clinical Nomenclature. *Circulation* 1979; 59:607–609
6. Falahati A, Sharkey SW, Christensen D, et al: Implementation of serum cardiac troponin I as marker for detection of acute myocardial infarction. *Am Heart J* 1999; 137:332–337
7. Antman EM, Grudzien C, Mitchell RN, et al: Detection of unsuspected myocardial necro-

- sis by rapid bedside assay for cardiac troponin T. *Am Heart J* 2002;133:596–598
8. Puleo PR, Meyer D, Wathen C, et al: Use of a rapid assay of subforms of creatine kinase MB to diagnose or rule out acute myocardial infarction. *N Engl J Med* 2002; 331:561–566
9. Myocardial infarction redefined—A consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *J Am Coll Cardiol* 2000; 36:959–969
10. Taniguchi T, Koido Y, Aiboshi J, et al: Change in the ratio of interleukin-6 to interleukin-10 predicts a poor outcome in patients with systemic inflammatory response syndrome. *Crit Care Med* 1999; 27: 1262–1264
11. Ueda S, Nishio K, Minamino N, et al: Increased plasma levels of adrenomedullin in patients with systemic inflammatory response syndrome. *Am J Respir Crit Care Med* 1999; 160:132–136
12. Stoiser B, Knapp S, Thalhammer F, et al: Time course of immunological markers in patients with the systemic inflammatory response syndrome: Evaluation of sCD14, sVCAM-1, sELAM-1, MIP-1 alpha and TGF-beta 2. *Eur J Clin Invest* 1998; 28:672–678
13. Hietaranta A, Kempainen E, Puolakkainen P, et al: Extracellular phospholipases A2 in relation to systemic inflammatory response syndrome (SIRS) and systemic complications in severe acute pancreatitis. *Pancreas* 2002; 18:385–391
14. Takala A, Jousela I, Olkkola KT, et al: Systemic inflammatory response syndrome without systemic inflammation in acutely ill patients admitted to hospital in a medical emergency. *Clin Sci (Lond)* 1999; 96: 287–295
15. Sablotzki A, Borgermann J, Baulig W, et al: Lipopolysaccharide-binding protein (LBP) and markers of acute-phase response in patients with multiple organ dysfunction syndrome (MODS) following open heart surgery. *Thorac Cardiovasc Surg* 2001; 49:273–278
16. Harbarth S, Holeckova K, Froidevaux C, et al: Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med* 2001; 164:396–340
17. Duffo F, Debon R, Monneret G, et al: Alveolar and serum procalcitonin: Diagnostic and prognostic value in ventilator-associated pneumonia. *Anesthesiology* 2002; 96:74–79
18. Angus DC, Linde-Zwirble WT, Lidicer J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
19. Marshall JC, Cook DJ, Christou NV, et al: Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995; 23:1638–1652
20. Ferreira FL, Bota DP, Bross A, et al: Serial evaluation of the SOFA score to predict out-

- come in critically ill patients. *JAMA* 2002; 286:1754–1758
21. Wilkinson JD, Pollack MM, Ruttiman, et al: Outcome of pediatric patient with multiple organ system failure. *Crit Care Med* 1986; 14:271–274
 22. Proulx F, Fagan M, Farrell CA, et al: Epidemiology of sepsis and multiple organ dysfunction syndrome in children. *Chest* 1996; 109:1033–1037
 23. Doughty LA, Carcillo JA, Kaplan SS, et al: Plasma nitrite and nitrate concentration and multiple organ failure in pediatric sepsis. *Crit Care Med* 1996; 109:1033–1037
 24. Leteutre S, LaCroix J, LeClerc F, et al: Pediatric Logistic Dysfunction Score. *Med Decis Making* 1997
 25. Carcillo JA, Task Force Members, Fields AI: Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Patients in Septic Shock. *Crit Care Med* 2002; 30:1–13
 26. Denoix PX: Enquete permanente dans les centres anticancereux. *Bull Inst Natl Hyg* 1946; 1:70–75
 27. Gospodarowicz M, Benedet L, Hutter RV, et al: History and international developments in cancer staging. *Cancer Prev Cont* 1998; 2:262–268
 28. Renaud B, Brun-Buisson C, ICU-Bacteremia Study Group: Outcomes of primary and catheter-related bacteremia: A cohort and case-control study in critically ill patients. *Am J Respir Crit Care Med* 2001; 163:1584–1590
 29. Opal SM, Cohen J: Clinical gram-positive sepsis: Does it fundamentally differ from gram-negative bacterial sepsis? *Crit Care Med* 1999; 27:1608–1616
 30. Ziegler EJ, Fisher CJ Jr, Sprung CL, et al: Treatment of Gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: A randomized, double-blind, placebo-controlled trial. *N Engl J Med* 1991; 324:429–436
 31. Wortel CH, von der Mohlen MAM, van Deventer SJH, et al: Effectiveness of a human monoclonal anti-endotoxin antibody (HA-1A) in gram-negative sepsis: Relationship to endotoxin and cytokine levels. *J Infect Dis* 1992; 166:1367–1374
 32. McCloskey RV, Straube RC, Sanders C, et al: Treatment of septic shock with human monoclonal antibody HA-1A: A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1994; 121:1–5
 33. Hausfater P, Garric S, Ayed SB, et al: Usefulness of procalcitonin as a marker of systemic infection in emergency department patients: A prospective study. *Clin Infect Dis* 2002; 34:895–901
 34. Damas P, Ledoux D, Nys M, et al: Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. *Ann Surg* 1992; 215:356–362
 35. Panacek EA, Kaul M: IL-6 as a marker of excessive TNF-alpha activity in sepsis. *Sepsis* 1999; 3:65–73
 36. Bernard GR, Vincent J-L, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
 37. Annane D, Sébille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and Fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871
 38. Vincent J-L, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996; 22:707–710
 39. Marshall JC, Panacek EA, Teoh L, et al: Modeling organ dysfunction as a risk factor, outcome, and measure of biologic effect in sepsis. *Crit Care Med* 2001; 28:A46
 40. Eli Lilly and Company: Briefing Document for XIGRIS for the Treatment of Severe Sepsis. http://www.fda.gov/ohrms/dockets/ac/01/briefing/3797b1_01_Sponsor.htm, August 6, 2001
 41. Cook R, Cook DJ, Tilley J, et al: Multiple organ dysfunction: Baseline and serial component scores. *Crit Care Med* 2001; 29:2046–2050