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EXPERT PANEL

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

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Abstract *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 Society of Critical Care Medicine (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:* 29 participants attended the conference from Europe and North America. In advance of the conference, subgroups were formed to evaluate the following areas: signs and symptoms of sepsis, cell markers, cytokines, microbiologic data, and coagulation parameters.. The present manuscript serves as the final report of the 2001 International Sepsis Definitions Conference. *Conclusion:* 1. Current concepts of sepsis, severe sepsis and septic shock remain useful to clinicians and researchers. 2. These definitions do not allow 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 non-specific. 4. An expanded list of signs and symptoms of sepsis may better reflect the clinical response to infection. 6. PIRO, a hypothetical model for staging sepsis is presented, which, in the future, may 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.

Keywords Sepsis · Severe Sepsis · Septic Shock · SIRS · PIRO

Introduction

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, 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 term "systemic inflammatory response syndrome" (SIRS). The term 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 clinical findings:

- Body temperature higher than 38°C or lower than 36°C
- Heart rate higher than 90/min
- Hyperventilation evidenced by respiratory rate higher than 20/min or $PaCO_2$lower than 32 mmHg
- White blood cell count higher than 12,000 cells/ μl or lower than 4,000/ μl

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. Because our goal was not to conduct a systematic review, the search strategy is not reported here.

Bone et al. [1] 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]. Early diagnosis and treatment may lead to improved survival in these critically ill patients. 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 concurrent increase in clinical trial data supported the need 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 (ATS), and the Surgical Infection Society (SIS). Each of the sponsors provided official representation at the conference and during the preparation of this manuscript.

Goals and methods of the conference

The overall goals of the conference were threefold and began with a review of the strengths and weaknesses of the current definitions of sepsis and related conditions. The second goal focused on 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 D.C. in December 2001 and included 29 participants from Europe and North America. Prior to convening, five subgroups were formed to evaluate the signs and symptoms of sepsis, cell markers, cytokines, microbiological data, and coagulation parameters. Subgroup participants corresponded electronically prior to 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 manuscript based on subgroup executive summary documents and the plenary sessions. Additional information was introduced for participant review after the conference via telephone conference, e-mail, and live discussions. This manuscript 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 (WHO) 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 WHO biochemical criterion for establishing the diagnosis of AMI was 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 have been introduced into clinical practice [6, 7, 8], and, as a result, 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 of the syndrome or in identifying a distinct pattern of host response [2, 3].

While the clinical manifestations of systemic inflammation are protean, the biochemical features may be more consistent. Investigators have detected elevated circulating levels of interleukin 6 [10], adrenomedullin [11], soluble CD14, soluble endothelial cell/leukocyte adhesion molecule 1, macrophage inflammatory protein 1α [12], extracellular phospholipase A_2 [13], and C-reactive protein [14] in patients meeting the 1992 SIRS criteria. In the future, if supported by further epidemiological data, it may be possible to use purely biochemical and/or immunological, rather than clinical, criteria to identify the inflammatory response. It may be that inflammation is present when the circulating concentration of interleukin 6, procalcitonin [15, 16, 17], or C-reactive protein is 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, for 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 to both 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 have defined infection as a pathological process caused by invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic micro-organisms. 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 definition of SIRS discussed above, we include 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

Table 1 Diagnostic criteria for sepsis

Infection[a]
Documented or suspected *and* some of the following[b]:
General parameters
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C
Heart rate >90 bpm or >2 SD above the normal value for age
Tachypnea: >30 bpm
Altered mental status
Significant edema or positive fluid balance (>20 ml/kg over 24 h)
Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes
Inflammatory parameters
Leukocytosis (white blood cell count >12,000/μl)
Leukopenia (white blood cell count <4,000/μl)
Normal white blood cell count with >10% immature forms
Plasma C reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic parameters
Arterial hypotension[b] (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
Mixed venous oxygen saturation >70%[b]
Cardiac index >3.5 l min^{-1} m^{-2}[c,d]
Organ dysfunction parameters
Arterial hypoxemia ($PaO_2/FIO2$ <300)
Acute oliguria (urine output <0.5 ml kg^{-1} h^{-1} or 45 mM/l for at least 2 h)
Creatinine increase ≥0.5 mg/dl
Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000/μl)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)
Tissue perfusion parameters
Hyperlactatemia (>3 mmol/l)
Decreased capillary refill or mottling

[a] Defined as a pathological process induced by a micro-organism
[b] Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children
[c] Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children
[d] Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C 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, elevated serum lactate level, and bounding pulses

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 should 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 question is whether thresholds similar in *degree* of abnormality confer similar *prediction* in sepsis.

During the deliberations on the signs and symptoms that characterize sepsis, the group turned toward the day-to-day "reality" for bedside clinicians. The group 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 a myriad of 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" (Table 1) 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 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 persons die annually in Europe and more than 200,000 in the United States [18].

Organ dysfunction can be defined using the definitions developed by Marshall et al. [19] or by the Sequential Organ Failure Assessment 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 Pediatric Multiple Organ Dysfunction and Pediatric Logistic Organ Dysfunction scores [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 mmHg (in children, less than 2 SD below normal for age); mean arterial pressure lower than 60, or a reduction in systolic blood pressure of more than 40 mmHg from baseline, despite adequate volume resuscitation, in the absence of other cause of 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 to central pulses, altered alertness, flash capillary refill or capillary refill longer than 2 s, 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 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 pathological involvement. For any given tumor type, survival tends to be correlated with certain TNM subgroups.

Using a variation of the TNM approach, we developed a classification scheme for sepsis – called **PIRO** – that stratifies patients on the basis of their ***P****redisposing conditions*, the nature and extent of the ***i****nsult* (in the case of sepsis, infection), the nature and magnitude of the host ***r****esponse*, and the degree of concomitant ***o****rgan dysfunction* (Table 2). It is important to emphasize that the PIRO concept is rudimentary; extensive testing and further refinement are 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 in influencing the risk of premature death from other common conditions, such as cancer and 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 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 can influence both the incidence and the outcome in similar or conflicting ways. They can 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 the person 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

Table 2 The PIRO system for staging sepsis

Domain	Present	Future	Rationale
Predisposition	Premorbid illness with reduced probability of short tem survival. Cultural or religious beliefs, age, gender	Genetic polymorphisms in components of inflammatory response (e.g., Toll-like receptor, tumor necrosis factor, interleukin 1, CD14); enhanced understanding of specific interactions between pathogens and host diseases	At the present, premorbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult depend heavily on genetic predisposition (future)
Insult (infection)	Culture and sensitivity of infecting pathogens; detection of disease amenable to source control	Assay of microbial products (lipopolysaccharide, 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, C-reactive protein	Nonspecific markers of activated inflammation (e.g., procalcitonin or interleukin 6) or impaired host responsiveness (e.g., HLA-DR); specific detection of target of therapy (e.g., protein C, tumor necrosis factor, platelet-activating factor)	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.,multiple-organ dysfunction syndrome, logistic organ dysfunction system, Sequential Organ Failure Assessment, Pediatric Multiple Organ Dysfunction, Pediatric Logistic Organ Dysfunction)	Dynamic measures of cellular response to insult – apoptosis, cytopathic hypoxia, cell stress	Response to preemptive therapy (e.g., targeting micro-organism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present

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 is 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 biological markers of response severity include circulating levels of procalcitonin [16, 33], interleukin 6 [34, 35] and many others. When a new mediator is identified, epidemiological studies are required to determine whether measurements of the compound can be useful for staging patients. Furthermore, the optimal set of biological markers for staging sepsis may depend upon 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 α (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 tumor necrosis factor, an early mediator in the inflammatory cascade, is more effective in patients without significant organ dysfunction [39], whereas drotrecogin α (activated) may provide more benefit to patients with

Table 3 The PIRO system for Staging Sepsis

Domain	Present	Future	Rationale
Predisposition	Premorbid illness with reduced probability of short tem survival. Cultural or religious beliefs, age, gender	Genetic polymorphisms in components of inflammatory response (e.g. Tlr, 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 of 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	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)	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
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 pre-emptive therapy (e.g. targeting micro-organism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present

greater as compared to 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 from 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 methodological 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 manuscript, we do 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 chose 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):

– 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 years ago.

– These definitions do not allow precise staging or prognostication of the host response to infection.
– While SIRS remains a useful concept, the diagnostic criteria for SIRS published in 1992 are overly sensitive and nonspecific.
– An expanded list of signs and symptoms of sepsis may better reflect the clinical response to infection.
– The operational definitions of sepsis may be refined and tested in the future as we increase our understanding of the immunological and biochemical characteristics of these conditions.
– We hypothesize that improvements in the management of critically ill patients with serious infections will 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 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.

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