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The ACCP-SCCM Consensus Conference on Sepsis and Organ Failure

United States Supreme Court Justice Potter Stewart once wrote, "I can't define obscenity, but I know it when I see it."[1] Until quite recently, that statement could equally well have been applied to sepsis and related disorders. Even in four recent multicenter trials, markedly different definitions of sepsis, shock, and organ failure were employed.[2-5]

From a clinical standpoint, the absence of firm definitions for these disorders has had—until now—little practical consequence because the only treatments available have been antibiotics and supportive care. Given the abundance of new agents under active investigation, however, more precise diagnostic guidelines are needed to allow us to evaluate efficacy, to determine which patients might benefit from such treatments, and to compare the results of different trials.

There are a number of historical reasons why firm definitions have been lacking:

1. Until roughly 30 years ago, sepsis, septic shock, and multiple organ failure were rarely seen. Simply put, we could not keep severely ill or injured patients alive long enough for these disorders to develop.

2. Many of the early studies of sepsis focused on patients with Gram-negative bacteremia. However, we now know that the majority of patients with sepsis are not bacteremic.

3. Many of the early studies were conducted in surgical patients or trauma victims; it was not clear whether the physiologic derangements that occurred in these patients were the same as those that occurred in patients with Gram-negative bacteremia.

4. The lack of precise criteria for the terms *infection*, *sepsis*, *sepsis syndrome*, and *septic shock* made it difficult to assess the severity of the infectious process and the differences between study populations.

5. The lack of precise criteria for the term *multiple organ failure* made it difficult to establish which organs were affected in patients with sepsis. It also made it more difficult to determine whether organ failure was a cause—or a consequence—of sepsis.

6. Only recently has the knowledge of the molecular and cellular events that occur in sepsis and its sequelae begun to shed light on the complex cascade of events underlying these disorders. Although our knowledge of these events is still incomplete, we have learned enough to make the need for more exacting definitions apparent.

7. There have not been enough epidemiologic studies to evaluate the systemic response to infection and its consequent sequelae of sepsis and multiple organ failure.

Last year, one of us (R. C. B.) published two articles[6,7] in an initial attempt to establish more uniform terminology. In subsequent commentaries, two of us (C. L. S. and W. J. S.) took issue with many of the original recommendations.[8,9] However, it quickly became clear that there was much we agreed on, and that there were many questions we all felt needed to be raised and answered. For example, is *sepsis* an appropriate term for a process that may take place in the absence of infection? Can *shock* be defined solely in terms of blood pressure? If the extent of organ dysfunction can vary, is it accurate to speak of organ "failure"? Each of us has attempted to use current terminology to address these questions, but we were, in essence, trying to fit square pegs into round holes. Because of this need, a consensus conference, sponsored by the American College of Chest Physicians and the Society of Critical Care Medicine, was held. On page 1644 of this issue, the consensus statement from that conference appears. The participants agreed that two new terms are necessary:

1. *Systemic inflammatory response syndrome* (SIRS): This term is preferred to *sepsis* when describing the widespread inflammation (or clincal response to that inflammation) that can occur in patients with such diverse disorders as infection, pancreatitis, ischemia, multiple trauma, hemorrhagic shock, and immunologically mediated organ injury. The term *sepsis*, a subcategory of the dysfunction newly defined as SIRS, should be used only for those patients with documented infection.

2. *Multiple organ dysfunction syndrome* (MODS): The extent of organ dysfunction in patients with SIRS can vary tremendously, both from patient to patient and within the same patient over time. The term *MODS* was coined to indicate the wide range of severity and the dynamic nature of this disorder. There are two relatively distinct (although not mutually exclusive) pathways by which MODS can develop: In primary MODS, there is a direct insult to the organ that becomes dysfunctional. Examples of such direct insults include gastric aspiration in the lungs or rhabdomyolysis in the kidney. This direct insult causes

an inflammatory response that is localized, at least in the beginning, to the affected organ. Secondary MODS is a consequence of trauma or infection in one part of the system that results in the systemic inflammatory response and dysfunction of organs elsewhere. An understanding of the etiology of organ dysfunction is important in the treatment of the underlying disease often present in MODS.

In addition, the consensus conference agreed on definitions for the terms *bacteremia, sepsis, severe sepsis, septic shock,* and other related disorders. In developing these definitions, another problem became apparent, particularly in light of recent clinical trials: We currently do not have a good way to predict which patients will develop SIRS or MODS. For example, many patients with severe infection (even bacteremia) never develop sepsis, while others with seemingly mild infections develop a massive systemic response. As yet, we do not know why. This inability to identify patients at greatest risk is currently causing problems for the researchers who design clinical trials and it will cause even greater problems as clinicians implement the innovative new treatments that are being developed to fight sepsis, SIRS, and MODS.

These new definitions of sepsis were developed to provide maximum flexibility in classifying patients for identification and treatment in both the clinical and research settings. For instance, a patient fulfills the criteria for sepsis when more than one of four criteria are present; one does not have to meet a set of specific and absolute criteria. For severe sepsis, sepsis must be present with either hypotension, hypoperfusion, or organ dysfunction. Although the new definition of sepsis may lead to the inclusion of patients with less severe disease into the category of sepsis, the definition entails the presence of a systemic inflammatory response and allows a differentiation of patients with sepsis from those with severe sepsis and organ system involvement. Such a differentiation would have a further base in different mortality rates.

New treatments, based on our understanding of the molecular and cellular mechanisms that underlie the systemic inflammatory response, are now being developed and tested. It seems reasonable to assume that these new treatments for sepsis are most likely to be effective if given as early as possible. But how do we avoid giving these agents unnecessarily to patients in little danger of developing SIRS or MODS? It is hoped that these new definitions will eventually allow clinicians to forecast which patients will develop more severe forms of the disease at an earlier stage of its progression.

Thus, another aim of the consensus conference was to assess the various "severity of illness" scoring systems for trauma and sepsis. It was the belief of the conference that the use of these scoring systems—in conjunction with the diagnostic criteria established for SIRS, MODS, and related disorders—may be the best available method for predicting which patients are at greatest risk. Obviously, research is needed to confirm (or refute) this belief and to elucidate how these scoring systems, which were designed to assess prognosis in large groups, can be used to predict outcome in individual patients.

The final task of the consensus conference was to provide recommendations on how these new definitions could be incorporated into the design of clinical trials for new treatments that can fight SIRS and MODS. In response to many of the concerns discussed above, the conference also sought to provide guidelines for the design of these trials.

This consensus statement is not the "last word" on these disorders. We must resign ourselves to the fact that these new criteria are not perfect. In a hypothetical example, during the study of a new therapeutic drug, the experimental treatment of a group of patients defined by these consensus criteria might demonstrate that the drug is not beneficial, with the result that it is discarded. Yet, with the use of a different set of criteria, the agent might be found to be beneficial. As we learn more about the cause of SIRS, it may become necessary to readjust our terminology. Such adjustments in language would be a small price to pay if we finally learn how to substantively improve outcome for patients with these disorders.

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The Management of Long-term Mechanical Ventilation at Home

Home care for patients requiring long-term mechanical ventilation will increase in the future as a suitable alternative for appropriately selected candidates.[1] However, after hospital discharge, clinical outcomes of life-supported children and adults have not been well documented. In this issue (see page 1500), Gilgoff et al have provided physicians and others caring for ventilator-assisted persons at home with some dramatic observations regarding the potential for medical instability depending upon pathophysiology, time of day, and approach to technique. In this study, clinically significant hypoventilation (associated with apnea and seizures) was observed in patients with high cervical spinal cord injuries who were receiving volume-controlled mechanical ventilation via uncuffed tracheostomy and volume-preset portable ventilator. The hypoventilation resulted from variable leaks around the tracheostomy due to different upper airway mechanics during sleep and wakefulness. Pressure support was used to compensate for the upper airway leaks and to achieve adequate ventilation.

The clinical observations of Gilgoff et al provide a strong message to all physicians regarding the need for rigorous initial and continuous evaluation of each long-term ventilated patient at home. Pressure support and other evolving techniques and technologies (noninvasive ventilation via nasal mask)[2] are examples of new approaches that may be suitable alternatives for patients requiring prolonged home mechanical ventilation. Both these newer techniques and more traditional methods (volume ventilation via tracheostomy) require strict selection criteria and outcome indicators to ensure safety, efficacy, and appropriateness for the quality management of a growing number of candidates being considered for home care.

The report by Gilgoff et al comes from a respiratory rehabilitation center of excellence with decades of home care experience.[3] Special regional centers can provide the components of an ideal environment for the initial preparation, education, and training of the ventilator-assisted person and family members.[4] In this clinically oriented research setting, observations can be made which can guide the medical management of ventilator-assisted patients at home.

Realities of cost and logistics of care today require that such data be applied by practitioners in the community. More physicians are becoming involved with the care of ventilator-assisted patients locally near their practice.[5] Monitoring technology now exists that could allow continuous measurements to be done using the home as a clinically suitable alternative to the hospital *provided that* an appropriately designed and managed system is available. This is desirable not only for convenience but also because family-centered care and monitoring at home permit involvement of the most consistent observers (ventilated persons and family members) in a natural setting under normal conditions and with the regular daily routine, which cannot be duplicated in a facility.

As the interest in home mechanical ventilation grows, the need of practicing physicians and others for more rigorous research regarding vital issues such as technology assessment and long-term management outcomes becomes more critical. Physicians do have some available consensus guidelines and recommendations for directing their care of patients in the home.[6-9] However, physicians continue to have major gaps of scientific knowledge about long-term ventilation and continue to face daily inadequacies in the organization of home care, which are disincentives for direct involvement in care in the home.

Five years ago, research activities and agendas regarding the scientific foundation, organization of care, and public policy research were proposed and discussed at a meeting concerning mechanical ventilation in the home at the National Institutes of Health. Since then, clinical studies such as the current observations by Gilgoff et al have been steps in the right direction. The value of these reported experiences further supports the need for those concerned about the future of long-term mechanical ventilation at home to address clinical and other vital investigational issues.

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