Inclusion Criteria for Clinical Trials in Sepsis*

Did the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Definitions of Sepsis Have an Impact?

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Over the last 25 years, a growing number of clinical trials have evaluated novel sepsis therapies. To promote uniformity in inclusion criteria for patient enrollment, the American College of Chest Physicians and Society of Critical Care Medicine first published consensus conference definitions for sepsis in 1992.

Many of the clinical trials in sepsis targeted specific mediators of the inflammatory cascade. The use of biomarkers of sepsis activity (ie, tumor necrosis factor-α and interleukin-1) may be the most ideal inclusion criterion for patient enrollment. Because rapid assays for meaningful biomarkers of activity are currently unavailable, investigators are forced to rely on clinical criteria for patient enrollment.

The American College of Chest Physicians
(ACCP) and Society of Critical Care Medicine (SCCM) held a consensus conference on the definitions of sepsis in August 1991 in Chicago, IL. The consensus conference definitions published in 1992 were intended to facilitate comparisons between clinical trials in sepsis by promoting uniformity of the inclusion criteria in research protocols.

To our knowledge, there has been no investigation of the impact of the consensus conference definitions on the inclusion criteria for sepsis trials. The purpose of this study was to characterize (1) the utilization of specific inclusion criteria for patient enrollment in sepsis clinical trials and (2) the impact that the consensus conference definitions have had on these criteria.

MATERIALS AND METHODS

We used the MEDLINE database to search the literature for the following keywords: sepsis; sepsis syndrome; septic shock; and septicemia. We limited the search to studies that were clinical trials, were performed in humans, were indexed in Index Medicus, and were published in English. We selected 25 years of the literature (10 years after the consensus conference [ACC] and 15 years before the consensus conference [BCC]) as a representative sample of the literature, yielding a total of 25 years of clinical trials (from 1976 to 2001). The citations included studies of innovative therapies, antimicrobial agents, pharmacodynamics, hemodynamic support, and supportive care. Both intervention and observational studies were included. We excluded studies of sepsis prevention.

Basic data of each of the clinical investigations were recorded, including the following: first author; year of publication; continent of origin; study design; and total number of patients. The data regarding inclusion criteria were abstracted by the following method. For studies that referenced or utilized (either verbatim or by adaptation) any previously published standard for their inclusion criteria, the source of the sepsis definition was recorded. If no predefined criteria were referenced or utilized, then the authors either (1) did not list any specific inclusion criteria for “sepsis,” or (2) used inclusion criteria that were dissimilar to previously defined sepsis criteria and therefore were presumed to have been generated de novo. The presence or absence of specific laboratory and physiologic variables in the inclusion criteria (ie, WBC count, temperature [T], BP or drop in BP, heart rate [HR], or respiratory rate [RR]) was abstracted from each study. We also recorded whether or not the sepsis trial (1) required positive blood culture results and (2) incorporated markers of acute organ dysfunction (ie, one or more of the following: cardiovascular instability; respiratory insufficiency; renal insufficiency; encephalopathy; or metabolic acidosis) into the inclusion criteria. In addition, for all studies (from 1976 to 2001), we recorded whether or not patient comorbidities or predisposing factors for sepsis were reported in the article.

Clinical trials published BCC (from 1976 to 1992) were compared with clinical trials published ACC (from 1993 to 2001). Statistical analysis was performed using the χ² test, and a p value of ≤ 0.05 was considered to be significant.

This study did not use human subjects. Protocols such as this without human subjects routinely receive a waiver of informed consent from the institutional review board at our hospital.

RESULTS

One hundred seventy-six clinical trials in sepsis (total number of patients, 25,130) were included. Fifty-seven trials were published BCC, and 119 were published ACC.

Clinical trials published ACC were more likely to reference or utilize (either verbatim or by adaptation) a previously published standard or definition in the inclusion criteria than those published BCC (65% vs 11%, respectively; p < 0.001). The consensus conference definitions were the standards utilized in 69% of the trials published ACC. The rest of the trials published ACC (31%) used the term sepsis syndrome, as defined by Bone et al.⁶

From 1987 to 1992, there were six studies published ACC that referenced or utilized standardized criteria for patient enrollment, each of which utilized and referenced the entry criteria for the methylprednisolone use in sepsis trial performed by Bone et al.⁷ None of the studies published BCC that had been published prior to the 1987 methylprednisolone trial referenced or utilized a previously published standard for inclusion criteria.

The utilization of specified values for WBC count, T, HR, and RR as inclusion criteria was significantly increased in the ACC group compared to the BCC group, as follows: WBC count, 62% vs 26%, respectively (p < 0.001); T, 89% vs 56%, respectively (p < 0.001); HR, 77% vs 26%, respectively (p < 0.001); and RR, 76% vs 28%, respectively (p < 0.001). Nine of 57 studies published BCC (16%) explicitly required blood culture positivity as an inclusion criteria vs 4 of 119 studies published ACC (3%; p < 0.006). None of the four studies published ACC that required blood culture positivity utilized predefined criteria for sepsis. Twenty-eight of 57 studies published BCC (49%) incorporated markers of organ dysfunction into the inclusion criteria vs 81 of 119 of the studies published ACC (65%; p < 0.03). A total of 20% of all studies (36 of 176 studies) published from 1976 to 2001 reported patient comorbidities or predisposing factors for sepsis in the article.
**DISCUSSION**

The ACCP and SCCM held a consensus conference on the definitions of sepsis in August 1991 in Chicago, IL. Although standardized inclusion criteria for sepsis trials had been utilized prior to this conference, there had been no consensus that these inclusion criteria should be adopted for research protocols. The consensus conference definitions published in 1992 were intended to facilitate comparisons between clinical trials in sepsis by promoting the uniformity of inclusion criteria in research protocols. This manuscript introduced a new term, systemic inflammatory response syndrome (SIRS), which validated the concept that the host response to infection (via endogenous mediators of the inflammatory response) was equally as important in sepsis as in the source of infection itself.

The consensus conference also produced definitions for sepsis in various stages. Sepsis was defined as infection plus two or more of the following SIRS criteria: T, > 38°C or < 36°C; HR, > 90/min; RR, > 20 breaths/min (or PaCO₂ < 32 mm Hg); or WBC count, > 12,000 cells/μL or < 4,000 cells/μL (or > 10% band forms). Severe sepsis was defined as sepsis plus organ dysfunction, hypotension, or hypoperfusion abnormalities, including lactic acidosis, oliguria, or encephalopathy. Septic shock was defined as sepsis-induced hypotension (ie, systolic BP, < 90 mm Hg or a drop of > 40 mm Hg in the absence of other cause of hypotension) plus hypoperfusion abnormalities despite adequate fluid resuscitation. The consensus conference also recommended a new focus on sepsis-induced organ dysfunction and introduced the term multiorgan dysfunction syndrome.

Recently, the proceedings of the second consensus conference on the definitions of sepsis were published. This was an international conference sponsored by the ACCP, the SCCM, the European Society of Intensive Care Medicine, the American Thoracic Society, and the Surgical Infection Society. The opinion leaders in that conference found that there were no data to support a change in the existing (1992) consensus conference definitions of sepsis. That conference also introduced the predisposition, infection/insult, response, organ dysfunction (PIRO) model, which was designed to be a staging system for sepsis, analogous to the TNM staging system for cancer. The PIRO model was intended to be a hypothesis-generating model for future research. In this study, 20% of all sepsis trials from 1976 to 2001 reported predisposing factors for sepsis.

The purpose of this study was to characterize (1) the utilization of specific inclusion criteria for patient enrollment in sepsis clinical trials and (2) the impact that the consensus conference definitions have had on these criteria. In this study, clinical trials published ACC were significantly more likely to reference or utilize standardized inclusion criteria, and the consensus conference definitions were the standards utilized in most of the ACC trials.

The term sepsis syndrome used in the study by Bone et al, which was a predecessor of the first consensus conference definitions, was the second most often utilized definition overall and appears to have been a key evolutionary step in establishing the current definitions. Although clinical trials published both BCC and ACC used definitions from the study of Bone et al, the incorporation of standardized inclusion criteria into clinical trials was not widespread until publication of the first consensus conference guidelines. One limitation of this study is that there is no way to know what impact the criteria of Bone et al would have had over the same time period if the consensus conference definitions never existed.

The sharp increase in the utilization of a previously published standard for patient enrollment is not only an indicator of the impact of the consensus conference, but may also be a surrogate for the standardization of inclusion criteria. However, our study did not look at uniformity directly. A study focusing on uniformity in patient enrollment would have required a comparison of comprehensive demographic data (including severity scores) from control arms of randomized trials published BCC and ACC. However, only 36 of 57 of clinical trials (63%) published BCC provided comprehensive demographics tables in the manuscript (compared with 10% of 119 trials [91%] published ACC), and only 19% of trials published BCC reported values for severity scores (compared to 76% of trials published ACC) in the results. Therefore, such a methodology was not possible.

Whether or not it is beneficial to have uniformity in laboratory or physiologic criteria (ie, SIRS criteria) is a matter of ongoing debate, because some authors are concerned that SIRS criteria may be too sensitive and may not be helpful in clinical practice or clinical trials design. Whether or not SIRS criteria should be incorporated into the definition of sepsis is still controversial. However, the sharp increase in the utilization of standardized inclusion criteria represents a major advance for clinical investigations in sepsis. This standardization helps to make scientific comparisons from one study to another.

More than 20 years ago, only patients with documented bacteremia had their clinical syndrome attributed to sepsis. Blood culture positivity, how-
ever, was not incorporated into the framework of the consensus conference definitions. Although a minority of clinical trials in both groups of this study required blood culture positivity in the trial inclusion criteria, clinical trials published ACC were significantly less likely to require documentation of bacteremia.

The consensus conference recommendations for a focus on sepsis-induced organ dysfunction may have had an important impact. Studies published ACC were significantly more likely to incorporate markers of acute organ dysfunction (ie, one or more of the following: cardiovascular instability; respiratory insufficiency; renal insufficiency; encephalopathy; or metabolic acidosis) into the inclusion criteria. These findings may indicate a paradigm shift away from a microbiological definition of sepsis toward a definition based on host response and organ dysfunction.

The findings of this study indicate that investigators are incorporating consensus conference definitions into research protocols. Therefore, opinion leaders should continue to strive for progress in defining sepsis. Future consensus conferences will likely continue to have an important impact on clinical trials as the definition of sepsis keeps evolving.

CONCLUSION

Since 1992, there has been a significant increase in the utilization of predefined sepsis criteria for patient enrollment in clinical trials, and this increase can be attributed to the existence of consensus conference definitions. When compared to the inclusion criteria published BCC, the inclusion criteria published ACC were less reliant on blood culture positivity and were more likely to incorporate markers of acute organ dysfunction.

REFERENCES