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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Background: **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.**
Study objectives: **To characterize (1) the utilization of specific criteria for patient enrollment in sepsis clinical trials and (2) the impact that the consensus conference definitions have had on these criteria.**
Design: **We used MEDLINE to identify clinical trials in sepsis from 1976 to 2001. Clinical trials published after the consensus conference (ACC; from 1993 to 2001) were compared with trials published before the consensus conference (BCC; from 1976 to 1992).**
Results: **We identified 176 clinical trials (ACC, 119 trials; BCC, 57 trials). Clinical trials published ACC were more likely to utilize or reference a previously published standard for inclusion criteria (65% vs 11%, respectively; $p < 0.001$). The consensus conference definitions were the standards used in 69% of these trials. The utilization of specified values for WBC count, temperature (T), heart rate (HR), and respiratory rate (RR) 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, respectively 76% vs 28% ($p < 0.001$). ACC, clinical trials were less likely to require blood culture positivity (4 of 119 trials [3%] vs 9 of 57 trials [16%] , respectively; $p < 0.006$) and were more likely to incorporate markers of acute organ dysfunction (81 of 119 trials [68%] vs 28 of 57 trials [49%], respectively; $p < 0.03$) in the inclusion criteria.**
Conclusions: **(1) 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. (2) Compared to inclusion criteria BCC, inclusion criteria ACC were less reliant on blood culture positivity and were more likely to incorporate markers of organ dysfunction.** ***(CHEST 2005; 127:242–245)***

Key words: clinical trials; sepsis; sepsis syndrome, septicemia; septic shock; severe sepsis

Abbreviations: ACC = after the consensus conference; ACCP = American College of Chest Physicians; BCC = before the consensus conference; HR = heart rate; PIRO = predisposition, infection/insult, response, organ dysfunction; RR = respiratory rate; SCCM = Society of Critical Care Medicine; SIRS = systemic inflammatory response syndrome; T = temperature

Over the last 25 years, a growing number of clinical trials have evaluated novel therapies for sepsis. Unfortunately, the definition of sepsis and the inclusion criteria for patient enrollment in sepsis clinical trials have been diverse. The effect of this diversity was evident in a wide disparity in control arm mortality rates for sepsis clinical trials in the 1980s,[1] and this diversity did not permit accurate comparisons between studies.

Many of the clinical trials in sepsis targeted specific mediators of the inflammatory cascade.[2–4] 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[5] 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 interventional 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 χ^2 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 BCC 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 (68%; $p < 0.03$). 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.

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