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SURVIVING SEPSIS CAMPAIGN: A CRITICAL REAPPRAISAL

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ABSTRACT—In 2002, the declaration of Barcelona launched a worldwide campaign that proposed to decrease in sepsis-related mortality by the introduction of evidence-based medicine into the management of sepsis. This paved the way for the publication of a wide selection of recommendations entitled the Surviving Sepsis Campaign (SSC) Guidelines. Whereas most of the medical community received the guidelines with enthusiasm, dissonant voices were made public just after its publication, and in recent years, the SSC guidelines were a source of intense debate, resulting in a recent revision of the guidelines. In the midst of a large controversy, it is evident that a critical reappraisal of the SSC guidelines is timely. In our opinion, whereas many relevant aspects of the SSC guidelines have been discussed, there are three major limitations that deserve a closer look, and they are sepsis as a public health issue, the weight of the evidence behind the recommendations, and the absence of recommendations related to the prevention of sepsis. In conclusion, although we recognize that the SSC is a valuable initiative, many of its present aspects must be revised to provide a clear message for clinicians taking care of sepsis patients at bedside. New guidelines should be based on solid evidence, have no interference from the pharmaceutical or medical equipment industry, and should have a stronger preventive and public health approach.

KEYWORDS—Sepsis, surviving sepsis campaign, severe infections, guidelines, multiorgan failure

INTRODUCTION

In October 2002, the declaration of Barcelona launched a worldwide campaign that proposed to decrease sepsis-related mortality by the introduction of evidence-based medicine into the management of sepsis. This paved the way for the publication of a wide selection of recommendations entitled the Surviving Sepsis Campaign (SSC) Guidelines (1). Whereas most of the medical community received the guidelines with enthusiasm, some dissonant voices were made public just after its publication. Criticism on the SSC was initially directed to ambiguous criteria used for grading the evidence of the recommendations that resulted in having "level A studies" that were not supported by two level 1 investigations (2, 3). Moreover, in the first version of the guidelines, ancillary therapies that are the cornerstone of good clinical practice in infectious diseases, such as the use of antibiotics or drainage of the source of infection, were considered level E of evidence because they were not based on randomized controlled trials (RCTs) (1). Recently, editorials questioned not only the adequacy of evidence grades but also the possibility of biases in the recommendations (4–6). Such biases were exemplified by the absence of measures tested in many RCTs such as selective digestive decontamination in the SSC guidelines (4), and, in addition , an excessive role of the pharmaceutical industry in the conception of the guidelines was suggested (7). A recent revised version of the guidelines was released (8), but many controversial aspects are still present (9, 10).

In the midst of a large controversy, it is evident that a critical reappraisal of the SSC guidelines is timely. In our opinion, although many relevant aspects of the SSC guidelines have been discussed (4) there are three major limitations that deserve a closer look, and they are the weight of the evidence behind the recommendations, the absence of recommendations related to the prevention of sepsis, and sepsis as a public health issue. The authors of the SSC guidelines state that sepsis is a relevant public health issue (1). However, despite the endorsement of several medical societies, the interventions proposed by the SSC guidelines have an excessive focus on individual health. Actually, late referral to the intensive care unit is a major issue, and the shortage of critical care beds, the difficulties in the recognition of sepsis, and its severity may contribute significantly to its exceedingly high mortality rates (11). In addition, delays in the correction of hypotension and in the initiation of adequate antimicrobial therapy are related to increased mortality of sepsis patients (12). Therefore, basic measures such as the facilitation of access to emergency departments and critical care units and training of primary care, emergency, and other healthcare professionals to the early diagnosis and treatment of sepsis are a crucial issue.

The prevention of both community-acquired and nosocomial sepsis is also largely neglected by the SSC. As a worldwide campaign, it should recognize the inequities of several different health systems and provide the scientific rationale and the recommendations for the prevention of sepsis. Community-acquired pneumonia is a major cause of sepsis that may be prevented by pneumococcal and influenza vaccines. Nosocomial sepsis is a major source of morbidity and mortality, and simple and cost-effective interventions have been proposed to decrease its frequency (13). Recent studies demonstrated that straightforward interventions coupled with continued education may virtually eradicate catheter-associated infections (13)

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and significantly decrease the rates of ventilator-associated pneumonia. Taken together, these measures should have a major public health impact.

Another disquieting issue is the weight of the evidence behind the SSC guideline recommendation. In fact, many of the present recommendations are derived either from a single large phase 3 study (usually interrupted for benefit) (14, 15) or from clinical trials performed on patients that did not necessarily had sepsis (16, 17) or with different degrees of sepsis severity (15). The prompt and general adoption of interventions based on phase 3 trials interrupted for benefit should be viewed with caution. Montori et al. (18) recently evaluated the epidemiology and reporting quality of these trials in a meta-analysis. In this study, the authors conclude that among the 143 studies evaluated, most were published in high-impact clinical journals during the last 15 years (18). Moreover, the reasons for the interruption were not clear or in accordance to the current recommendations in most studies. In an accompanying editorial, Pocock (19) observed that a strict policy should be applied for the adequate interruption of phase 3 trials for benefit because an inadequate early interruption may result in the observation of a small number of adverse events or false-positive results. The critical care literature has many examples of pharmacological interventions with a good scientific rationale and reasonable preclinical and phase 2 results that failed to show survival benefit in subsequent trials (20, 21). Recently, a large RCT tested the hypothesis that the use of a tissue-factor pathway inhibitor (Tifacogin) can reduce the mortality of patients with severe sepsis (22). Despite the encouraging results and statistically significant reduction in mortality (29% vs. 39%; $P = 0{,}006$) present in the first interim analysis, the study was not interrupted for benefit. At the completion of patient inclusion according to the original design, no survival benefit could be demonstrated (22). In the Protein C Worldwide Evaluation in Severe Sepsis study, the use of drotrecogin-α reduced mortality in patients with severe sepsis; however, recent studies demonstrate an excess of bleeding (23) or no benefit when used in different populations of patients with sepsis (24, 25). When studies are interrupted for early benefit or when the indications of a pharmacological intervention are changed/expanded, phase 4 confirmatory studies should be performed (26).

The SSC recommendations also include several interventions that were not specifically tested in patients with sepsis, including deep venous thrombosis and stress ulcer prophylaxis (1, 8). Given that critical illnesses encompass a wide range of clinical disorders with a surplus of diverse physiological derangements, can the results of successful interventions in critical care be generalized to all severely ill patients? The recent Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial (27) clearly showed that the answer is no, and intensive insulin therapy makes an excellent example. Undoubtedly, results of the surgical patients' trial (16) are impressive, and strong biological rationale and data are available to support the beneficial effects of insulin infusion and glucose control (28). Nevertheless, patient selection is still a crucial, but often neglected, matter. The Leuven trial involving medical patients (29) had already shown less impressive results when compared with surgical patients (16), and only post hoc analysis can find benefit in a selected (>3 days of intensive care unit stay) group of patients (29). Moreover, it is evident from the trials' data that the most prominent effects of insulin therapy are the prevention of new organ failure and infection (16). Such results make one wonder if insulin can be helpful in patients who are perhaps already too sick. In the VISEP trial (27), patients had a high hospital mortality rate when compared with the Leuven trial (16) and were more severely ill and had a higher number of organ dysfunctions at entry. Furthermore, safety issues arise from the VISEP trial because an exceedingly high rate (12.1%) of hypoglycemia is present in the intervention group (10, 27). A closer look is necessary to clarify whether the insulin infusion protocol used is harmful or the population of patients with sepsis has peculiar clinical aspects (renal and liver dysfunction) that would increase the susceptibility to hypoglycemia. Therefore, solid data on sepsis patients are needed before a wide judicious recommendation for any medical intervention in acutely ill septic patients is made. The need for confirmatory studies and careful patient selection in sepsis becomes even more important in light of the results from recent trials. In the Corticosteroid Therapy of Septic Shock (CORTICUS) study, patients with severe sepsis who use hydrocortisone did not decrease mortality or improve organ dysfunction (30). However, patients in the CORTICUS study were less severely ill than those evaluated in the previous French multicenter RCT, and improved survival was observed in patients with septic shock and adrenal insufficiency (15). Moreover, higher rates of adverse events such as hyperglycemia and nosocomial infection were present in those treated with hydrocortisone in the CORTICUS study (30).

In conclusion, although we recognize that the SSC is a valuable initiative, many of its present aspects must be revised to provide a clear message for clinicians taking care of sepsis patients at bedside. New guidelines should have no interference from the pharmaceutical or medical equipment industry, and these should have a stronger preventive and public health approach. Early cost-effective interventions (12, 31) and the prevention of community-acquired and nosocomial sepsis should be highlighted. In addition, we think that more data on the pathophysiology of sepsis are essential. This should emerge from well-designed preclinical studies (32) and from studies involving clinical data and biomarkers of severity (33–35) that may identify patients that can benefit from specific therapeutic interventions.

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