The Surviving Sepsis Campaign Guidelines: Should We Follow?

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Epidemiological studies have shown that the incidence of sepsis has increased over the past few decades [1,2]. In Israel, about 4000 patients with the diagnosis of sepsis are admitted every year to hospitals owned by Clalit Health Services (the largest of the four health insurance funds in the country). In addition, the admission of these patients to the intensive care unit has increased by 40% over the last 7 years [3]. The mortality related to sepsis remains high, with sepsis being the leading cause of death in non-cardiac ICUs. With a view to improving outcomes by standardizing care, the first Surviving Sepsis Campaign developed evidence-based guidelines that were published by the American and European Societies of Intensive Care in 2004 [4]. Indeed, for the first time, a disease with high mortality was targeted for a systematic process and outcome improvement worldwide.

In view of the assertion that the Surviving Sepsis Campaign was simply a sophisticated marketing campaign of a major pharmaceutical company and to address the issue of uncertainty and academic conflict, further meetings for revision of the guidelines were convened in 2006 [5]. These meetings were conducted without commercial support and using a GRADE system of rating the quality of evidence and an independent determination of strength of recommendations. The paper by Carny and co-authors [6] in this issue of *IMAJ* deals with the new recommendations, in particular, with four areas that underwent revision based on new data, namely glucose control, the use of low dose steroids and drotrecogin alfa (recombinant activated protein C), and issues relating to the feeding of critically ill patients.

In addition, science is changing some of the recommendations like a pendulum: the best example is glucose control. If the Van den Berghe studies in 2001 [5] determined 80–110 mg/dl as the best limit to treat, new issues such as the rate of hypoglycemia, variability, continuous measurements [6] and risks versus benefits have changed these limits several times, increasing it to 180 and decreasing it again to 100–150 mg/dl, and today the guess is more frequent than a precise answer.

A further area of controversy concerns the use of low dose corticosteroids, which has yielded contradictory results in trials and recent meta-analyses. In an attempt to shed further light on the matter, two recent papers have attempted to assess their efficacy and safety using Bayesian methodology, which interprets the concept of probability as a measure of a state of knowledge. This is in contrast to interpreting it as a frequency or a propensity of some phenomenon (frequentist statistics), which must be either true or false. In the first paper, 2 abstracts and 12 published papers were included in the meta-analysis [7]. The authors concluded that while a null effect for mortality treatment efficacy was not excluded, there remained a high probability of treatment efficacy. In addition, on average, older participants had increased odds of mortality under steroid treatment and the log odds mortality under steroid therapy decreased as the underlying risk of mortality increased. In contrast to this study, the authors of the second paper [8], using only randomized trials from three published meta-analyses, found that low dose steroids were not associated with survival benefits (defined as a relative risk reduction of > 15–25%). In addition, for all the analyses, there was a high probability of the development of steroid-induced side effects, including super-infections, bleeding and hyperglycemia. In view of the lack of conclusive data, and as suggested by Sprung et al. in a recent special article [9], it would seem prudent to use steroids only in patients with severe septic shock and the presence of a systolic blood pressure vale of < 90 mmHg for more than 1 hour. Finally, there appears to be no justification for using steroids in patients with severe sepsis but without evidence of shock, or in patients stabilized with fluids and vasopressors.

Parenteral nutrition is another example of important differences between the American and European societies. According to the Society of Critical Care Medicine [10], a patient not able to receive enteral feeding could wait 7 to 10 days until complementary parenteral nutrition could be administered since no prospective controlled study exists demonstrating the contrary. Inversely, the European society ESPEN guidelines [11] recommend

ICU = intensive care unit

giving parenteral nutrition after 48 hours if the patient will not tolerate enteral feeding, based on the fact that starvation and undenourishment are deleterious for ICU patients. This is also based on the treatment regimens available in the United States and elsewhere. This example of two very different recommendations based on the same literature is very instructive for the ongoing discussions on guidelines.

While the recombinant form of activated protein C, drotrecogin alpha activated, was the first agent to have shown mortality reduction in sepsis (6.4%) [12], its use has been increasingly criticized. Thus, a recent Cochrane Database review found no evidence suggesting that DAA should be used for treating patients with severe sepsis or septic shock [13]. However, many experts believe that DAA should be used only in patients who have received optimal care, i.e., patients who are severely ill and have persistent or new organ dysfunction after adequate guideline-based hemodynamic resuscitation. In this regard, a recent study from the U.S. found that patients with septic shock who received DAA and whose management was based on current sepsis management guidelines had a reduced in-hospital mortality rate compared to patients with similar acuity who were not treated with DAA [14]. It should be recognized that one of the major drawbacks to the use of DAA, besides its high financial cost, is the high incidence of bleeding, which may be as high as 10%. Until more data are available, it seems appropriate that DAA be used in patients with a high risk of death despite optimal care and without any contraindications.

Despite these and other ongoing treatment controversies, recent evidence suggests that implementation of the Surviving Sepsis Campaign bundle positively impacts clinical outcome. Thus, a national educational program in Spain based on these guidelines [15] resulted in a decrease in mortality in the post-intervention cohort (44.0% vs. 39.7%, $P = 0.04$). A study conducted in surgical ICUs found that the outcome in surgical septic shock patients was significantly related to the number of fulfilled therapeutic guidelines included in a sepsis bundle [16]. Finally, an international guideline-based performance improvement program showed that compliance with the Surviving Sepsis Campaign bundle was associated with an improved adjusted odds ratio for mortality (absolute drop of 5.4% over 2 years), which improved the longer a site was in the campaign [17]. When this group examined the relationship between bundle targets and hospital mortality, they found that administration of broad-spectrum antibiotics, obtaining blood cultures before their initiation, and maintaining blood glucose control were all associated with lower hospital mortality. In addition, both the administration of drotrecogin alfa in the first 24 hours was associated with improved survival in those with shock, and achieving plateau pressure control in patients requiring mechanical ventilation improved outcome. There was no association between mortality and the use of low dose steroids.

It thus appears that we should indeed be following current management guidelines. However, implementation is difficult to achieve and its success may be dependent on appointing local leaders to champion the project, actively involving relevant stakeholders and benchmarking. The need for continuing education is also essential. The Israel Intensive Care Society is ideally placed to take up the challenge.

DAA = drotrecogin alpha activated

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