Ongoing debate: The “Surviving Sepsis Campaign”, the ESICM and Eli Lilly

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Recently, the European Society of Intensive Care Medicine, in its role as one of the founding societies, felt obliged to respond to severe criticism [1,2] with regard to the Surviving Sepsis Campaign (SSC) and the financial involvement of the pharmaceutical industry [3]. The SSC was set up in 2002 as an initiative of the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM) and the International Sepsis Forum (ISF). In 2004, the SSC published 46 guidelines on the treatment of severe sepsis and septic shock [4]. These concerned 18 interventions for adult patients (Table 1), with the aim of reducing sepsis-related mortality worldwide by 25% before 2009. The main sponsor of the SSC was Eli Lilly, the manufacturer of activated protein C (aPC). The guidelines gave aPC a grade B recommendation for the treatment of sepsis. This elicited a lot of criticism which concentrated mainly on three issues. First, that the substantial financial support from Eli Lilly could lead to manipulation of the SSC guidelines for their own profit. Second, the rating system of the guidelines was said to be suboptimal, with an overreliance on large randomized, controlled trials (RCTs). Third, the negative side effects of activated protein C (aPC) were neglected in the guidelines.

The ESICM statement responded mainly to the first issue, which is also the most severe allegation of all i.e. the suggestion that the SSC guidelines are no more than a promotional activity by Eli Lilly. Everyone, including the ESICM in its statement, will agree that, because of potential financial conflict of interest, it is preferable that the process of drawing up guidelines should not be sponsored by pharmaceutical companies. However, quite a number of measures were taken by both the SCC and the ESICM to secure this process. Furthermore, it must unfortunately be acknowledged that other streams of funding are very difficult to obtain, even for scientific societies.

According to the ESICM statement, no industrial representatives were present at either the original guideline development meeting or the revision meeting, and all the recommendations included in the SSC guidelines reflected an evidence-based appraisal of the available data. Furthermore, the ESICM’s official journal Intensive Care Medicine, strongly debated the recommendations of the SSC. Other precautions that were taken, but not mentioned in the ESICM statement, are the detailed publication of the financial support by pharmaceutical companies, the lack of financial compensation for investigators and authors for the time spent on the development of the guidelines, the publication of the SSC guidelines in peer-reviewed journals and the collaboration with 10 other esteemed international scientific societies in the field of intensive care medicine and infectious diseases, including the SCCM and the ISF.

However, despite all these measures and despite the fact that the aPC guideline was only one of 46 guidelines developed by the SSC, severe and disproportionate criticism persists and the guidelines have probably not been accepted and implemented as widely as the SSC had planned and hoped for. Many clinicians will have no doubt about the probity of the SSC and the integrity of the scientific societies involved. However, to their credit, the ESICM and the SSC have decided to take several additional measures to end all the controversy surrounding future guidelines and to maintain credibility. The ESICM now insists on the compulsory disclosure of potential conflicts of interest for all candidates for all posts in the Society. Furthermore, an association between ESICM, the American Thoracic Society and the SCCM has been formed in order to develop clear guidelines for ongoing relationships with industry and the handling of any conflicts. It should be noted that the SSC is currently re-evaluating the guidelines without any financial support from the pharmaceutical industry, which they hope will lead to a broader acceptance among clinicians.

We share the concerns with regard to the second criticism i.e. the suboptimal rating system of the guidelines with its overreliance on RCTs [1]. The highest grades (A, B and C) of recommendation can only be obtained if RCTs have been performed. One single RCT only can result in a grade B guideline (Table 2). However, literature shows that multiple RCTs may lead to controversial results. Furthermore, RCTs, even when large numbers of patients are included, can have severe limitations. They may be of unblinded design (e.g. intensive insulin therapy studies [5]) or the study population may be not identical to those of interest to the guideline panel (e.g. stress ulcer prophylaxis studies [6]). Observational studies can only obtain a low rating, but sometimes yield extremely large and consistent estimates of the magnitude of a treatment effect (e.g. initial antibiotic therapy). Also on rare occasions, all plausible biases from observational studies may be working to underestimate an apparent treatment effect.

There is, therefore, a growing need for an updated or new rating system that does not rely on RCTs, which is now being developed by the international GRADE group [7].

The third criticism concerns the aPC guideline (failure to discuss a persisting concern regarding the effectiveness of aPC, the risk of bleeding and omission of the results of new aPC trials) which seems to be exaggerated, since the guideline is in line with currently available evidence.

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The main comment is that the beneficial effect of aPC has only been shown in a subgroup of the original study population in the PROWESS trial [8].

However, this subgroup was defined before starting the trial on pathophysiological grounds (treatment effects dependent of severity of illness, subgroups divided in quartiles of APACHE score). Follow up of the PROWESS population confirmed the beneficial effect of aPC on mortality in this subgroup after 1 and 2.5 years [9]. Unfortunately however, without a good reason, a confirmatory second trial has not been performed, particularly since this single RCT was terminated prematurely due to excessive mortality in the placebo group [8]. In our view the first trial evaluating a new treatment should never be stopped prematurely because of efficacy. It should only be stopped prematurely in the event of harm.

Another comment was the omission of the possible magnitude of the increased risk of serious bleeding due to aPC in the ENHANCE trial [10] in the guideline supplement, published in Critical Care Medicine of November 2004. However, the risk of serious bleeding was documented in this supplement, but during aPC infusion, and not cumulatively during and after infusion. Most serious episodes of bleeding took place after aPC infusion, and were, therefore, probably related to a higher incidence of haematological organ failure in the ENHANCE population and were not caused by aPC. It would have been appropriate to mention these data in the guideline. Nevertheless, according to the PROWESS and ENHANCE data, the risk of serious bleeding appears to be low, since the calculated number needed to harm of fatal intracranial bleeding is 250 [11].

Another omission in the guideline supplement in the November issue of Critical Care Medicine 2004, was the results of the ADDRESS trial [12]. These data were presented during an ESICM meeting 10 to 13 October 2004, and the authors of the guidelines were probably familiar with the results. But then again, by this time the November issue of Critical Care Medicine had already gone to press. Furthermore, this trial just confirmed that aPC had no beneficial effect on the mortality of patients who, according to the data of the PROWESS study, did not have a reason for treatment with aPC.

When taking into account the consistent data regarding survival with aPC in the ENHANCE study as well as the results of longer follow-up of the PROWESS study and the low risk of fatal intracranial bleeding, the recommendation in the SSC guidelines to treat patients with severe sepsis and at high risk of death, with aPC, is therefore, in line with the currently available evidence.

Conclusion

The drawing up of guidelines should preferably not be sponsored by the pharmaceutical industry. However, the allegation that the SSC guidelines are no more than a promotional activity by Eli Lilly is out of perspective, considering all the measures that have been taken to secure the objectivity of the guidelines particularly as the recommendation on aPC is in line with currently available evidence. We agree with the criticism that the rating system used for the SSC guidelines is suboptimal and is overreliant on RCTs. Therefore, for the revision of the guidelines, another rating system, such as the approach formulated by the international GRADE group should be considered.

To end the controversy surrounding the SSC guidelines and the financial sponsorship of Eli Lilly, the SSC and the ESICM in cooperation with the AMC in Amsterdam.

Conflict of interests

Both authors declare they have no conflict of interests. The Department of Intensive Care at the UMC, chaired by Professor Girbes, received a grant from Eli Lilly a year ago for a trial with aPC, in collaboration with the AMC in Amsterdam.

References


