

## Editorial

# An Opinion Too Far—The Campaign Against the Surviving Sepsis Campaign

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The Surviving Sepsis Campaign (SSC) was inaugurated in 2003 with the stated goal of reducing death from sepsis by one-third by the end of the decade. Among the eleven sponsoring organizations is the Surgical Infection Society (SIS); the inauguration of the campaign and its stated goals were lauded in these pages at the time [1]. Since then, evidence-based guidelines for the treatment of sepsis have been published [2], and tools for implementation, data collection, and measurement of process improvement have been disseminated.

Never before has a disease entity with such a high rate of death as severe sepsis/septic shock been targeted for systematic process and outcome improvement worldwide. The SSC has been embraced enthusiastically, judging from organized national and international participation. Other organizations (The Institute for Healthcare Improvement's [IHI] Saving 100,000 Lives Campaign, VHA's Transformation of the ICU) have been stimulated by the SSC's aims to undertake similar evidence-based quality improvement programs to enhance the care of critically ill patients.

Such an ambitious, worldwide undertaking as the SSC requires clinical expertise, administrative structure, and funding. Expertise has come from innumerable content experts in sepsis who are committed to improving the care of sepsis patients worldwide. Administration has come via an SSC Steering Committee populated by the three lead organizations, the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum

(ISF). Funding, being unavailable from peer-reviewed sources and beyond the means of the not-for-profit educational organizations that organized the campaign, came from industry, primarily Eli Lilly and Company (Lilly). Funding by industry, and Lilly in particular, has led some to call the entire SSC into question, considering that Lilly markets a drug (recombinant human activated protein C, rhAPC) for sepsis that is mentioned in the guideline. In the October 19, 2006, issue of *The New England Journal of Medicine* (NEJM), Eichacher et al. published a diatribe against what they perceived to be undue influence exerted by Lilly on the SSC, and specifically its evidence-based guideline [3]. Media coverage was immediate and fawning [4–6] (as readers of this space could predict [7]), but transitory. Apparent distortions of fact in their opinion piece [3], and the fact that NEJM has given those authors a platform to express their opinion on multiple occasions [3,8], raises questions of objectivity on the part of Eichacher et al. and NEJM.

In considering these questions, let us examine the article that raises the questions anew. Probably everyone who treats sepsis or belongs to an infection- or critical care-related organization will have an opinion as to the efficacy of rhAPC and SCC. Your editorial writer is no exception, and has relevant knowledge as well as potential conflicts of interest. By way of full disclosure, this writer was an officer of SIS when SIS joined SSC, and was then a Councilor and is now an officer of SCCM. Your editor has served as a consultant to and received honoraria from Lilly and from VHA for their Trans-

formation of the ICU campaign (which includes a “sepsis bundle”), and published on the use of rhAPC in surgical patients [9].

However, let us be perfectly clear. The opinions contained herein are my personal opinions, and mine alone. These opinions are not those of SIS, SCCM, SSC, VHA, Lilly, or any other entity. Content from the article by Eichacher et al. is reproduced in italics:

*. . . pharmaceutical and medical device companies have begun to invest in influencing the adoption of guidelines that serve their own financial goals. A case in point is the development of guidelines for the treatment of sepsis, which was orchestrated as an extension of a pharmaceutical marketing campaign. Although its advocates viewed this effort as an important approach to reducing sepsis-related mortality, the campaign appears to have usurped guideline development for commercial purposes. . . [3].*

The guideline document itself speaks to process: “The process [guidelines development] represented Phase II of the Surviving Sepsis Campaign, an international effort to increase awareness and improve outcome in severe sepsis. Meeting expenses as well as staff support for guidelines creation were provided by unrestricted industry educational grants as listed. There were no industry members of the committee. There was no industry input into guidelines development and no industry presence at any of the meetings. Industry awareness or comment on the recommendations was not allowed. The sponsors of the educational grants did not see the recommendations until the manuscript was peer reviewed and accepted in publication in final form.” [2].

*Although such [randomized, controlled] trials represent the gold standard of medical evidence, overreliance on them in the construction of guidelines has a tendency to favor new drugs and devices, which typically undergo at least one such trial in order to obtain governmental approval. [3].*

Is this carefully crafted statement anti-guideline, or simply a criticism of the SSC guideline? An argument can be made that it is the former.

Evidence-based medicine is just that—reliance on evidence. The randomized, controlled trial is accepted widely as the best-quality evidence available. Are the authors really suggesting that such trials are relied on excessively, or that older, less-rigorous evidence may be more reliable than contemporary randomized trials? What should be the alternative? Expert opinion? The accumulated experience of individual practitioners? If so, I bid a fond adieu to evidence-based medicine and the identification of best practices to standardize processes and improve care.

*In this instance, that reliance meant that rhAPC was given a highly favorable rating (grade B), whereas established therapies for sepsis (such as antibiotics, fluids, and vasopressors), though included in the recommendations, received lower ratings (grade D or E), because most had not undergone randomized, controlled trials owing to a lack of equipoise. [3].*

This sentence, of which Hawthorne himself would be proud, is in the opinion of the writer the most disingenuous statement in the paper of Eichacker et al. Guidelines parse their recommendations on the basis of the strength of the underlying evidence, not the perceived attractiveness of the recommendation. Rather than being “highly favorable” (the authors do not mention the five grade A recommendations contained in the SSC campaign document), a grade B recommendation is just that, usually derived from a single randomized, controlled trial, which was appropriate for rhAPC at the time the guidelines were developed and published. The readership of this journal will note with interest that surgical source control received a grade E recommendation in the SSC guideline, not because the authors believed it was unimportant, but because source control has not been (and is unlikely to be) subjected to a randomized trial.

*This imbalance is made more troubling by the campaign’s failure to discuss persisting concern about rhAPC, which has been reinforced by recent trials. [3].*

Aside from disputing whether an “imbalance” exists at all, the SSC is not a debating so-

ciety. There are other venues for that (apparently including NEJM). Nor is a guideline intended to replicate the technique of continuous meta-analysis, wherein the conclusions of the analysis have the fluidity to reflect each new study as it is published. Moreover, the recommendation for rhAPC is but one of more than 50 contained in the SSC guideline document, the continuous updating of which would be Herculean (not to mention expensive, but who, after all, would pay)? One of the substantial limitations of guidelines in general is the stasis inherent in periodic updates. Data must be collected and evidence graded, so that experts can parse the recommendations. It is anticipated that the SSC guideline will be updated in 2007. Time will tell what will be said about rhAPC, but there may be no change, because the rules of evidence for guideline construction still permit a grade B recommendation based on an existing single Class I trial.

Consider also whether Eichacher et al. are pursuing their own agenda, abetted by NEJM and their positions as senior investigators at The National Institutes of Health (NIH), and the ethics involved therein. They have had the privilege of criticizing rhAPC twice (once directly, once indirectly) in the pages of NEJM [3,9]. They have disseminated their opinion about rhAPC widely and repeatedly [3,8,10–14]. Although they disavowed any official status of their opinions by virtue of their employment, their relationship with NIH unavoidably provides cachet, especially with the media and the public [4–6]. By publishing their opinion (not new data) repetitively on the same subject, the appearance of objectivity is lost, and it can be argued that advantage is taken of their positions at NIH and their access to the editorial pages of esteemed journals.

Is NEJM itself a paragon of objectivity? One may argue not, for not only were Eichacher et al. afforded a second opportunity to express their opinion in the journal [3,9], but there is historic evidence of a decided anti-industry bias on the part of its editorial leadership. Each of its two immediate past editors-in-chief has published a book for the mass market that is critical of the pharmaceutical industry, its marketing practices, and its relationships with physicians [15,16].

Considering everything, Eichacher et al. and NEJM have carried their opinion too far, so as to obscure what is important—advancing knowledge and facilitating best practices in the provision of health care. The debate is not likely to end soon, or here, so we must regain our collective focus. Improvements in clinical care require change in both clinicians' behavior and medical care delivery systems. Evidence-based practice guidelines have been promulgated as a way to improve care and reduce unnecessary variation in clinical practice [17]. More than 1,800 "best practice" guidelines have been listed by the National Guidelines Clearinghouse [18], but there is little evidence that clinical care has improved as a result [19]. Innumerable barriers prevent adoption [20]. The methods employed by SSC were adapted from strategies championed by leading healthcare improvement organizations (such as IHI), including promoting greater awareness of the problem of severe sepsis and septic shock by clinicians and patients alike. Established, testable diagnostic and treatment criteria resulted from evidence-based development of care bundles. Process changes enabled by the guidelines and bundles can be documented for quality improvement.

The missing piece is funding. Despite evidence of the disconnect between knowledge and performance, public funding for guideline development/implementation has been diverted. In 2001, Congress authorized \$50 million/year for general patient safety research through the Agency for Healthcare Research and Quality, funds that were diverted subsequently to information technology research. Health services research was at once legitimized and then starved [21].

The SSC is a well-intentioned approach to transfer knowledge from bench to bedside and to improve the processes of care. The SSC provides essential tools for change and facilitates measurement and reporting of progress. It is folly to criticize broadly the evidence-based methodology and the guidelines and bundles that have resulted. Much harm could be done if nascent improvement-minded institutions cease their efforts. The premises of the SSC remain valid; SSC should press forward with the resources available.

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