Surviving Sepsis Campaign Guidelines: Selective Decontamination of the Digestive Tract Still Neglected

To the Editor:

We read with interest the guidelines for the management of severe sepsis and septic shock published in the March 2004 issue of Critical Care Medicine by the Surviving Sepsis Campaign (1). The authors claim to have used evidence-based medicine methodology; however, their major aim was consensus to increase awareness and to improve outcome in severe sepsis.

The authors of the Surviving Sepsis Campaign selected 19 interventions, including bicarbonate therapy, deep venous thrombosis prophylaxis, and considerations for limitation of support. Currently, there are five evidence-based medicine maneuvers showing a survival benefit in the intensive care unit (ICU) (Table 1). Only one maneuver is supported by at least two level 1 investigations, providing level 1 evidence with a grade A recommendation, and that is selective decontamination of the digestive tract (SDD) (2, 3). The other four are supported by only one trial, providing a grade B recommendation (4–7). SDD can be administered to all patients at risk of infection, in contrast, the other four only in specific subsets of ICU patients.

We were at a loss to explain the omission of the SDD intervention in the Surviving Sepsis Campaign guidelines, despite the availability of 54 randomized, controlled trials with seven meta-analyses showing a significant reduction of infectious morbidity and mortality (8). The rationale behind the maneuver of SDD is the observation that critically ill patients develop infection with their own gut microorganisms and that enteral antimicrobials in combination with early administration of parenteral antibiotics improve survival in critically ill patients (9). A major difference between the only parenteral antibiotic use and SDD is that enteral antibiotics also impact the flora of the oropharynx and gut, whereas systemic agents only treat the lungs, blood, and bladder.

Was SDD not considered by the Surviving Sepsis Campaign because some experts assert that it causes antimicrobial resistance, in particular, methicillin-resistant Staphylococcus aureus (MRSA)? Two individual trials of SDD (2, 3) showed that there was significantly less carriage and infection resulting from the resistant isolates among the target microorganisms aerobic Gram-negative bacilli in the group receiving SDD. SDD, by design, is not active against MRSA, and six studies suggested a trend toward a higher MRSA infection rate among ICU patients receiving SDD (10–15). SDD requires monitoring using surveillance cultures of the throat and rectum. These cultures also detect carriage of MRSA in an early stage, allowing the addition of enteral vancomycin to the classic SDD protocol. Four studies (16–19), among which two were randomized, controlled trials, support this approach. The concerns of experts that SDD, including SDD, that contribute to the prevention and treatment of this important clinical syndrome. We are confident that SDD will be incorporated in the dynamic, electronic, Web-based guideline process of the Surviving Sepsis Campaign.

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Table 1. Intensive care unit interventions that reduce mortality

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<thead>
<tr>
<th>Intervention</th>
<th>Relative Risk (95% CI)</th>
<th>Absolute Mortality Reduction, % (95% CI)</th>
<th>No. Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low tidal volume (4)</td>
<td>0.78 (0.65–0.93)</td>
<td>8.8 (2.4–15.3)</td>
<td>11</td>
</tr>
<tr>
<td>Activated protein C (5)</td>
<td>0.80 (0.69–0.94)</td>
<td>6.1 (1.9–10.4)</td>
<td>16</td>
</tr>
<tr>
<td>Intensive insulin (6)</td>
<td>0.44 (0.36–0.81)</td>
<td>3.7 (1.3–6)</td>
<td>27</td>
</tr>
<tr>
<td>&gt;5 days</td>
<td>0.52 (0.33–0.84)</td>
<td>9.6 (6.3–16.1)</td>
<td>10</td>
</tr>
<tr>
<td>Steroids (7)</td>
<td>0.90 (0.74–1.09)</td>
<td>6.4 (4.8–7.6)</td>
<td>16</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>0.83 (0.66–1.04)</td>
<td>10.8 (1.9–23.6)</td>
<td>9</td>
</tr>
<tr>
<td>Selective decontamination (3)</td>
<td>0.65 (0.49–0.85)</td>
<td>8.1 (3.1–13)</td>
<td>12</td>
</tr>
</tbody>
</table>

CI, confidence interval.


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The authors reply:
Dr. Viviani and colleagues provide an important perspective on selective decontamination of the digestive tract in the intensive care unit. They make valid points about the evidence supporting the use of this intervention. Why intensivists on both sides of the Atlantic have not embraced this approach is a complex issue related to tolerability, cost, effect of microbial flora, and impact on patient survival. The Surviving Sepsis Guidelines focuses primarily on the recognition and management of sepsis. Prevention of infection is equally important, but the authors of the Surviving Sepsis Guidelines chose to focus this document on diagnosis and management.

Admittedly, the document does include some management recommendations, such as those related to stress ulcer prophylaxis and deep vein thrombosis prophylaxis that are designed to reduce complications. Selective decontamination of the digestive tract could have been considered similarly. However, a comprehensive discussion of preventive strategies might have included topics ranging from proper hand hygiene to intravenous catheter management to isolation techniques. Guidelines focusing on such measures are available from the Society of Critical Care Medicine and from the Infectious Disease Society of America (1–3). However, we would agree that a focus on a comprehensive package for preventing intensive care unit infections, including selective decontamination of the digestive tract, would be a welcome guidance that clinicians would benefit from in preventing infections, including sepsis.

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Do Not (Over) Resuscitate

To the Editor:

Although Webster’s Dictionary defines resuscitate as “to return to life or to revive or to give mouth-to-mouth breathing technique to help a person to start breathing again,” the term has seen an increasing use outside that narrow definition in the medical literature in the past few years. The most recent example is the Surviving Sepsis Campaign Guidelines for the Management of Severe Sepsis and Septic Shock, which is published in the March 2004 issue of Critical Care Medicine (1). The authors talk of “initial resuscitation” and define “resuscitation goals” as certain numbers of central venous pressure, mean arterial pressure, urine output, or central venous or mixed venous oxygen saturation. Especially in the critical care literature, the term “volume resuscitation” is now commonly used. Parallel to that development, I noticed a growing confusion among health care providers about do-not-resuscitate (DNR) orders. This confusion is highlighted by two comments I recently received. One is from a critical care nurse who asked why a patient is in the intensive care unit at all, although his status is DNR. Another one is from an internal medicine colleague who asked about a patient who was treated in the surgical intensive care unit for severe septic shock with “volume resuscitation” according to the discharge summary and wanted to know why and when we had done cardiopulmonary resuscitation on that patient who had a clear DNR order. Although the use of the term resuscitation might indicate the urgent need of a treatment approach in a critical care setting and the early goal-directed treatment of sepsis, for example, has definitely been shown to increase the survival rate among those patients, we might even revive some cells in a literal sense but definitely not by the original definition of the term resuscitation. The danger of misinterpretation of DNR orders based on uncritical use of the term resuscitation in conjunction with common treatment options like volume replacement toward a “do not care order” outweighs the benefit of reinforcing certain aspects of the treatment strategy or protocol as urgent in a scientific text. Authors and editors should, therefore, avoid the use of the term resuscitation outside its original meaning of cardiopulmonary resuscitation.

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REFERENCE


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The authors reply:

We appreciate Dr. Schulz-Stubner’s viewpoint as expressed in his Letter to the Editor. We agree the word “resuscitation” currently has different meanings. Although Dr. Schulz-Stubner presents a Webster’s Dictionary definition, there is even disagreement among dictionaries as to how resuscitation and resuscitate are defined. For example, Stedman’s Medical Dictionary, 26th edition, lists several definitions of resuscitation (1), the first being “revival from potential or apparent death,” with the second being “cardiopulmonary resuscitation (CPR) defined as restoration of cardiac output and pulmonary ventilation following cardiac arrest and apnea, using artificial respiration and manual closed chest compression or open chest cardiac massage.” The first definition would allow the use of the term “volume resuscitation” as we used it in the Guidelines because patients with severe sepsis/septic shock have the potential for death. The second definition favors Dr. Schultz-Stubner’s choice. The American Heritage College Dictionary lists “resuscitate” definitions as first “to revive consciousness, vigor, or life to” and second to “regain consciousness” (2). Roget’s II The New Thesaurus, 3rd edition. Boston, Houghton Mifflin, 1997 lists resuscitation as “the act of reviving or condition of being revived: reactivation, rebirth, renaissance, resurrection, reawakening, revival, and revivification” (3). We would even add that the words “reanimation” or “reanimazione” are still currently used in France and in Italy, respectively, to refer to critical care medicine as a whole! Likewise, “intensive care units” are still called “unités de réanimation” in France. The primary reason is historical; before the development of modern medicine, all these measures had the common goal to simply restore life, that is, to “resuscitate.”

We agree that today the use of the word resuscitation in “volume resuscitation” and “do not resuscitate” is confusing and offers the potential for consternation among medical students, the layperson, and other healthcare professionals not well versed with how these terms are typically used. We sympathize with Dr. Schulz-Stubner in this regard, but we will have to do the best we can with the current language.

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Doing Antithrombin III An Injustice?

To the Editor:

We read with great interest the recent publication by Dr. Dellinger and colleagues (1), published in the March 2004 issue of Critical Care Medicine, about the suggested guidelines for the management of severe sepsis and septic shock and would like to express our appreciation for the endeavor of this group to try to propose a standardized approach for the treatment of critically ill patients with severe sepsis and septic shock. However, we are a little bit disturbed regarding their conclusion that antithrombin III (ATIII) should not be used in patients with sepsis based on the Kypersett study results.

The Kypersett trial is a randomized clinical trial that investigated the efficacy and safety of a high-dose ATIII therapy vs. placebo in patients with severe sepsis. The primary endpoint in this study was
not reached. However, in a prospectively defined subgroup of patients not receiving concomitant heparin, the 90-day mortality analysis showed a nominally significant survival benefit for those patients who had received high-dose ATIII (2). Although this is a lower level of evidence, it should be considered in the whole spectrum of levels of evidence from grades A to E and I to V (1).

On the other hand, the failure of the high-dose ATIII trial might be attributed to a potentially suboptimal study design. The intent of the protocol was to administer high-dose ATIII as early as possible, but the study design made it possible, rather likely, that high-dose ATIII would not be administered until very late after the onset of severe sepsis and organ failure, a time when therapy, in general, has little potential benefit. The data to revisit this hypothesis, sadly, are unavailable.

Studies in primates and other preclinical experiments showed ATIII to be very promising (3). Many smaller studies of ATIII in severe sepsis in humans have showed consistent results with matching decrease (approximately 25%) in 28-day mortality (4, 5). We have unpublished data on 81 patients who show a 14% absolute decrease in 28-day mortality.

Furthermore, despite an increase in the incidence of bleeding with high-dose ATIII in the Kybersept trial, the drug did not significantly increase overall mortality. This could suggest that the negative effect of bleeding was offset by a positive effect of high-dose ATIII on mortality.

We believe that totally dismissing the use of ATIII in severe sepsis based on the Kybersept trial alone might be doing ATIII an injustice. We think that the recommendations given by Dr. Dellinger and colleagues (1) for ATIII should be revisited.

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The authors reply:

We would like to thank Dr. Eid for his positive comments regarding the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock (1). The recommendation regarding use of antithrombin in severe sepsis and septic shock was based on the best evidence available at the present time. Dr. Eid was a coauthor of the Kybersept study, which was a double-blind, placebo-controlled, multicenter phase 3 trial of antithrombin in 2314 adult patients (2). The primary efficacy outcome was 28-day all-cause mortality in randomized patients who received any study drug and whose survival status after 28 days was known. Subpopulations of special interest were predefined and included the use of concomitant heparin. Mortality at 28 days was not significantly different in the subgroups of patients who received antithrombin or placebo and no heparin. Mortality at 90 days in patients who did not receive concomitant heparin (n = 680) was not a primary analysis and, according to the study statistical plan, was of descriptive and exploratory nature. Heparin use was not part of the randomization process, and caution is warranted in interpreting a post hoc, nonrandomized analysis. From a statistical standpoint, and in the absence of a multifactorial design, it makes no difference if a subgroup is prospectively defined or part of a post hoc analysis, that is, there is only one a priori primary analysis group.

Analysis of subpopulations in large sepsis trials of potential therapeutic agents should not be used to advocate use of an agent. Several phase 3 trials have used subpopulation analyses to conduct subsequent trials with disappointing results (3-5). In the opinion of the committee, the subpopulation analysis mentioned by Dr. Eid in the Kybersept study is not sufficient to warrant a recommendation for use of antithrombin in severe sepsis or septic shock.

Preclinical studies with antithrombin in animals and small clinical trials of antithrombin in patients have resulted in mixed results. Eiselle et al. found no improvement in mortality with use of antithrombin in a placebo-controlled, randomized, double-blind phase 2 multicenter clinical study in 42 patients with severe sepsis (6). They also performed a metaanalysis that included two other double-blind, placebo-controlled trials with antithrombin with a total of 122 patients with severe sepsis. They found a reduction in 30-day all-cause mortality of 22.9% in patients treated with antithrombin, but this result was not statistically significant. Multiple investigators have called for a sufficiently powered placebo-controlled phase 3 trial of antithrombin to assess any potential benefit. Certainly, the Kybersept study of more than 2000 patients provides the highest level of evidence currently available.

Although the question of interaction of heparin and antithrombin is intriguing, any hypothesis on use of antithrombin without concomitant heparin in severe sepsis should be subjected to appropriate investigation with a high-quality clinical trial that is adequately designed and sufficiently powered to determine whether antithrombin has beneficial effects.

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