permitted more rapid titration of the study drug dose rate, compared with the previous phase II study (2), because the latter study indicated that the effect of 546C88 on MAP occurs rapidly in response to a change in dose. More frequent adjustment of dose provided the possibility of tighter hemodynamic control, as is traditionally practiced when administering other vasoactive agents such as norepinephrine.

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DOI: 10.1097/01.CCM.0000131205.75130.DC

Stress Ulcer Prophylaxis

To the Editors:

The Surviving Sepsis Campaign guidelines (1) sponsored by critical care organizations around the world represent a remarkable collaborative achievement. In addition to providing a comprehensive template for clinicians to follow when managing the septic patient, the guidelines provide a scoring system that allows us to better understand the strength of evidence supporting these interventions. Although most of the recommendations accurately describe the available body of evidence, at least one therapy appears to have been given more credit than the literature would warrant.

Section Q states that "stress ulcer prophylaxis should be given to all patients with severe sepsis." The support for its grade A recommendation is that "although no study has been performed specifically in patients with severe sepsis, large trials confirming the benefit of stress ulcer prophylaxis in general ICU populations have included significant numbers of septic patients." Four studies are cited in support of this recommendation.

By definition, a grade A recommendation required two large randomized trials with clear-cut results. If the question is whether an added intervention is beneficial, these studies should be placebo controlled. In determining the necessity of stress ulcer prophylaxis, these studies do not exist.

Three of the cited studies were published in the 1980s and included a total of 352 patients. There was no control arm in any of the studies. pH control was the primary end point of the second largest trial. The 1998 study was a large well-designed trial that compared sucralfate with ranitidine in 1,200 mechanically ventilated patients. However, only 6% of patients had sepsis listed as the primary diagnosis, and there was again no control arm. The strongest support for stress ulcer prophylaxis would appear to be a 1991 meta-analysis where the authors determined that overt bleeding was reduced by antacids and H-2 blockers, whereas clinically important bleeding was reduced only with H-2 blocker prophylaxis, when compared with placebo (2). Thus, the available literature would seem to only support a grade C recommendation.

Since the publication of that meta-analysis, many things have happened. Several prospective trials in critically ill patients have described comparable rates of bleeding and endoscopic evidence of stress-related injury between treatment and placebo groups (3–5). Risk stratification for stress-related hemorrhage within the intensive care unit has been better defined. Proton pump inhibitors have become more widely used in the critical care setting.

Thirteen years ago, the authors of the meta-analysis questioned whether general improvements in managing the critically ill patient had already substantially reduced the risk of stress-related hemorrhage, independent of prophylaxis. Given the large number of proven interventions that have since been incorporated into managing the septic patient, one can argue that most of the early studies of stress ulcer prophylaxis are now obsolete. Now would seem the time to readdress this issue and perform the appropriately designed trial to determine whether stress ulcer prophylaxis is still required in 2004 and, if so, what the agent of choice is. Then, when these guidelines are later updated, we can have a recommendation that has earned its grade A rating.

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DOI: 10.1097/01.CCM.0000130833.92258.B9

Central Venous and Mixed Venous Oxygen Saturations in the Surviving Sepsis Campaign Guidelines

To the Editor:

The Surviving Sepsis Campaign guidelines (1) recommend in A.1. and A.2 a central venous *or* mixed venous oxygen saturation of ≥70% (a grade B

recommendation), yet in the 263-patient study (2) that is the basis for these recommendations, only central venous catheterization is used, and it is specifically pointed out in the Discussion section of that study (2) that the mixed venous oxygen saturation can be 5–13% lower than the values obtained from the central vein. What is the basis for the equivalence of central venous and mixed venous oxygen saturations in recommendations A.1. and A.2.?

The guidelines grade recommendations H.1.a. and H.1.d. as "E" [supported by nonrandomized, historical controls, case series, uncontrolled studies, or expert opinion, as outlined in the Methods section of the guidelines (1)], yet these recommendations are based on a 300-patient, placebo-controlled, randomized, double-blind study (3). If the previously mentioned 263-patient study (2), which was neither placebo-controlled nor blinded, leads to a grade B recommendation, why are recommendations based on a study with more patients, double-blinding, and placebo control (3) only grade E?

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DOI: 10.1097/01.CCM.0000130832.32725.B2

The authors reply:

We appreciate the insightful and constructive comments of Drs. Štefanec and Dr. DePriest. Dr. Štefanec points to our use of the same threshold for both central venous and mixed venous oxygen saturation despite studies that have demonstrated mixed venous oxygen saturation to be lower than central venous oxygen saturation in the shock state. These studies, however, included only patients with hypovolemic, cardiogenic, and late septic shock (1, 2). Another study performed in a wide variety of critically ill intensive care patients demonstrated essentially no clinical difference between the two values, but again not in patients with early septic shock (3). As yet, unpublished data (personal communication, Konrad Reinhart) performed in patients with septic shock do support that the target for mixed venous oxygen saturation should be 5–8% lower than the central venous oxygen target. Assuming publication of that data, the next edition of the guidelines are likely to recommend that variation in threshold for mixed venous oxygen saturation.

Dr. Štefanec also points out that the steroid recommendation for septic shock is graded lower than would occur if it was based purely on the Annane et al. study (4). The Annane et al. study enrollment criteria for patients with severe septic shock required systolic blood pressures <90 mm Hg for an hour despite vasopressors. Therefore, in that patient population, the recommendation would have been a grade A if the same dosage regimen was used. The committee believed that most septic shock patients encountered in the intensive care unit would not meet this severe of an entry criteria but still would potentially benefit from steroid therapy. The entry criteria for the smaller Bollaert et al. (5) and Briegel et al. (6) studies required vasopressors only and showed trends in mortality decreases as well as significance in nonmortality clinical outcomes. Since this latter population represents a group of patients more likely to be encountered in clinical practice, and in order to provide the best opportunity for steroids to make a difference in outcome, the final decision was a downgraded level of evidence to capture this more commonly encountered patient population. It should also be noticed that the dosage and route of administration as expressed capture the dose ranges and routes of administration from all three studies.

The "some experts" comments that follow the primary steroid recommendation were necessitated by the inability of the committee to achieve total agreement on any of these four areas (as expressed in the article introduction). Although H.1.a and H.1.d would be considered grade B from the Annane et al. study, the primary recommendation H.1 is broader than the Annane et al. patient population, and since there was no uniformity of agreement among the committee, by default it received a grade E. Although the short adrenocorticotropic hormone stimulation test nonresponders defined the population of benefit in the Annane et al. study, this test does not study the entire hypothalamic-pituitary axis, and some committee members had concerns about standardization of testing across centers. Although fludrocortisone (a mineralocorticoid) was used in the Annane et al. treatment regimen and is designated as optional in the SSC recommendations (note that the published SSC recommendation mistakenly lists fludrocortisone dosing as 50 μg orally "four times per day" and it should be "once a day"), animal studies indicate that it is the glucocorticoid that is important in improving clinical outcome in septic shock (7). In addition, hydrocortisone does have mineralocorticoid activity. Statements H.1.b and H.1.c. are based on recent nonrandomized trials, and a grade E is appropriate.

Dr. DePriest correctly points out that the references for the stress ulcer prophylaxis recommendation do not include placebo-controlled trials. The references were mistakenly lifted from the larger article to be published as part of a supplement on the guidelines and were intended to provide examples of stress ulcer prophylaxis studies that both had a breakdown of enrolled patient categories and showed a significant percentage of sepsis patients studied. The correct references are listed here (8–10). Even with the proper references from placebo-controlled trials, including a meta-analysis of placebo-controlled trials and a study showing superiority of H2 receptor antagonists, Dr. DePriest's points are well taken and our methodology for this grading could be debated. One could take the position that the placebo-controlled clinical trials used to support the value of stress ulcer prophylaxis are not large enough to engender an A grade and that a grade C would be more appropriate. Also making two separate recommendations, one for use of stress ulcer prophylaxis and one for choice of agent, may be more practical as it would allow different grading for each. These options will be considered in the next revision of the guidelines. We also agree that a randomized trial at this point in time to evaluate the role of stress ulcer prophylaxis would be appropriate.

R. Phillip Dellinger, MD, Jean Carlet, MD, Herwig Gerlach, MD, Dider Keh, MD, Andrew Rhodes, MD, Mitchell Levy, MD, For the Surviving Sepsis Campaign Management Guidelines Committee

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DOI: 10.1097/01.CCM.0000130827.34908.0A

Quality of Life After Mechanical Ventilation

To the Editor:

We read with interest the recent research article by Dr. Chelluri and colleagues (1), who described long-term mortality and quality of life after 48 hrs of continuous in-hospital mechanical ventilation. We have reported the results of a 1-yr postdischarge follow-up study of long-term mechanical ventilator patients (2) and were interested to find that although Dr. Chelluri and colleagues' results showed some similarity with our work, there were some differences worth noting.

First, and foremost, the definition of "long-term" mechanical ventilation continues to be unstandardized (3). Dr. Chelluri and colleagues defined prolonged mechanical ventilation as ≥48 hrs, whereas we defined it as >96 hrs of continuous mechanical ventilation. Based on pilot work, we had identified a significant difference in morbidity and mortality rates between patients ventilated for 48 vs. 96 hrs (unpublished analyses). As a result of those analyses, we selected >96 hrs of mechanical ventilation as our definition of prolonged mechanical ventilation for our study. Thus, there are most likely inherent differences in the subject pools of these two studies, with Dr. Chelluri and colleagues capturing a healthier cohort than the subjects in our study. This difference in eligibility criteria may explain the differences reported in the two studies.

Another difference between the studies is that Dr. Chelluri and colleagues followed subjects for 1 yr after eligibility into the study; we followed patients for 1 yr after hospital discharge. Given the variability in hospital length of stay associated with this patient population, the data obtained 1 yr after being eligible to enter the study (measured from the initiation of ventilation) no doubt yielded varying postdischarge time points and captured subjects at different points along the postdischarge continuum.

In addition to these differences, there are two outcome results that we wish to highlight. First, Dr. Chelluri and colleagues reported 1-yr SF-36 mental component scores similar to the general population and physical component scores that were worse than the population. Similarly, we found poor physical functioning (using the Sickness Impact Profile) up to 1 yr postdischarge, including a 1-yr cumulative mortality rate of 66.1%. However, unlike Dr. Chelluri and colleagues, we found poor psychosocial functioning 1 yr postdischarge along with poor quality of life scores.

Second, like Dr. Chelluri and colleagues, we found that a majority (78.8%) of patients who survived were residing at home 1 yr later. However, we also found that 21.2% of our patients were still residing in an institutional setting 1 yr after hospital discharge and that 63.6% of our patients spent time in an institutional setting before going home. We found that even 1 yr after discharge, many patients still needed substantial daily care from a caregiver when they were finally able to return home. Our patients, overall, had a difficult postdischarge course with poor quality of life 1 yr after discharge. Despite these differences, we agree with Dr. Chelluri and colleagues that there is a continued need to study this patient population and share study results with families and health care providers who are involved in treatment decisions and posthospital planning. In addition, we believe some of the differences between Dr. Chelluri and colleagues' findings and ours stem from the different enrollment criteria; the prognostic significance of requiring mechanical ventilation by day 3 or 4, vs. day 2, warrants further investigation.

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DOI: 10.1097/01.CCM.0000130826.54927.95

Paralysis During Mechanical Ventilation in Acute Respiratory Distress Syndrome: Back to the Future?

To the Editor:

We read with interest the article by Dr. Gainnier and colleagues (1) on the effects of neuromuscular blocking agents (NMBA) on oxygenation of heavily sedated, mechanically ventilated patients with the acute respiratory distress syndrome (ARDS). The authors observed significantly higher Pa_{O_2}/F_{IO_2} values in paralyzed patients but could not determine an obvious explanation for the increase in arterial oxygenation. We have comments regarding the utility and advisability of heavy sedation and muscle paralysis in patients with ARDS.

Both Dr. Gainnier and colleagues (1) and Freebairn (2) addressed a survey noting that 98% of responding hospitals used muscle paralysis in patients with ARDS (3). It is noteworthy that this survey was performed in 1990, a few years before the introduction of a new genera-