4. Kobayashi A, Nakatani M, Furuyoshi S, et al: In vitro evaluation of dextran sulfate cellulose beads for whole blood infusion low-density lipoprotein-hemoperfusion. *Ther Apher* 2002; 6:365–371

DOI: 10.1097/01.CCM.0000153594.30487.26

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 enteral vancomycin, promotes vancomycin-resistant enterococci and MRSA resistant to vancomycin have been refuted by eight studies (16, 18–24), of which five were randomized (19, 20, 22–24).

Systemic broad-spectrum antibiotics are administered to a high proportion of ICU patients, promoting the emergence of antimicrobial resistance. During the interventions of low tidal volume, glucose control, steroids, and activated protein C, the problem of nosocomial infections resulting from resistant microorganisms continued to grow. We believe that SDD may be part of the solution of the resistance problem for two reasons. First, the SDD intervention is underpinned by regular surveillance of gut flora. The chance to detect resistance in gut flora is five times higher than in diagnostic samples of the lower airways, urine, and blood (25). Second, gut overgrowth guarantees the presence of resistant mutants, which are selected by only parenteral antibiotic use through salivary and biliary excretion. The newer, even more potent systemic antimicrobials fail to clear MRSA and *Pseudomonas aeruginosa* from the gut, because the salivary and fecal concentrations are not lethal. The addition of enteral antimicrobials eliminates the source, controlling resistant mutants in the gut flora. We believe that the assertion that SDD causes resistance is misplaced in this era of evidence-based medicine.

In conclusion, the optimal management of severe sepsis and septic shock is complex and will represent a real challenge for the future as long as we are prepared to consider all interventions, 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

Intervention	Relative Risk (95% CI)	Absolute Mortality Reduction, % (95% CI)	No. Needed to Treat
Low tidal volume (4)	0.78 (0.65–0.93)	8.8 (2.4–15.3)	11
Activated protein C (5)	0.80 (0.69–0.94)	6.1 (1.9–10.4)	16
Intensive insulin (6)	0.44 (0.36–0.81)	3.7 (1.3–6)	27
>5 days	0.52 (0.33–0.84)	9.6 (3–16.1)	10
Steroids (7)	0.90 (0.74–1.09)	6.4 (−4.8–17.6)	16
Nonresponders	0.83 (0.66–1.04)	10.8 (−1.9–23.6)	9
Selective decontamination (3)	0.65 (0.49–0.85)	8.1 (3.1–13)	12

CI, confidence interval.

REFERENCES

1. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
2. Krueger WA, Lenhart F-P, Neeser G, et al: Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients: A prospective, stratified, randomized, double-blind, placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2002; 166:1029–1037

3. de Jonge E, Schultz M, Spanjaard L, et al: Effects of selective decontamination of the digestive tract on mortality and acquisition of resistant bacteria in intensive care: A randomised controlled trial. *Lancet* 2003; 363: 1011–1016
4. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
5. Bernard GR, Vincent J-L, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:799–709
6. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 245:1359–1367
7. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in a patient with septic shock. *JAMA* 2002; 288: 862–871
8. Liberati A, D'Amico R, Pifferi S, et al: Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care (Cochrane Review). *In:* The Cochrane Library, issue 1. Chichester, John Wiley & Sons, 2004
9. van Saene HKF, Petros AJ, Ramsay G, et al: All great truths are iconoclastic: Selective decontamination of the digestive tract moves from heresy to level 1 truth. *Intensive Care Med* 2003; 29:677–690
10. Gastinne H, Wolff M, Delatour F, et al: A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. *N Engl J Med* 1992; 326:594–599
11. Hammond JMJ, Potgieter PD, Saunders GL, et al: Double-blind study of selective decontamination of the digestive tract in intensive care. *Lancet* 1992; 340:5–9
12. Ferrer M, Torres A, Gonzalez J, et al: Utility of selective decontamination in mechanically ventilated patients. *Ann Intern Med* 1994; 120:389–395
13. Lingnau W, Berger J, Javorsky F, et al: Selective intestinal decontamination in multiple trauma patients: Prospective, controlled trial. *J Trauma* 1997; 42:687–694
14. Wiener J, Itokazu G, Nathan C, et al: A randomized, double-blind, placebo-controlled trial of selective digestive decontamination in a medical-surgical intensive care unit. *Clin Infect Dis* 1995; 20:861–867
15. Verwaest C, Verhaegen J, Ferdinande P, et al: Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients in a multidisciplinary intensive care unit. *Crit Care Med* 1997; 25: 63–71
16. Silvestri L, Milanese M, Oblach L, et al: Enteral vancomycin to control methicillin-resistant *Staphylococcus aureus* outbreak in mechanically ventilated patients. *Am J Infect Control* 2002; 30:391–399
17. Sanchez M, Mir N, Canton R, et al: The effect of topical vancomycin on acquisition, carriage and infection with methicillin-resistant *Staphylococcus aureus* in critically ill patients: A double-blind, randomized, placebo-controlled study. 37th ICAAC 1997, Toronto, Canada, Abstract J-117:310
18. de la Cal MA, Cerdà E, van Saene HKF, et al: Effectiveness and safety of enteral vancomycin to control endemicity of methicillin-resistant *Staphylococcus aureus* in a medical/surgical intensive care unit. *J Hosp Infect* 2004; 56:175–183
19. Silvestri L, van Saene HKF, Milanese M, et al: Prevention of MRSA pneumonia by oral vancomycin decontamination: A randomised trial. *Eur Respir J* 2004; 23:921–926
20. Sanchez M, Mir N, Canton R, et al: Incidence of carriage and colonization of vancomycin-resistant enterococcus (VRE) in intubated patients receiving topical vancomycin. 37th ICAAC 1997, Toronto, Canada, Abstract J-119:310
21. Bhorade SM, Christenson J, Pohlman AS, et al: The incidence of and clinical variables associated with vancomycin-resistant enterococcal colonization in mechanically ventilated patients. *Chest* 1999; 115:1085–1091
22. Arnow PA, Caradang GC, Zabner R, et al: Randomized controlled trial of selective decontamination for prevention of infections following liver transplantation. *Clin Infect Dis* 1996; 22:997–1003
23. Zwaveling JH, Maring JK, Klompmaker IJ, et al: Selective decontamination of the digestive tract to prevent postoperative infection: A randomized placebo-controlled trial in liver transplant patients. *Crit Care Med* 2002; 30: 1204–1209
24. Hellinger WC, Yao JD, Alvarez S, et al: A randomized, prospective, double blinded evaluation of selective bowel decontamination in liver transplantation. *Transplantation* 2002; 73:1904–1909
25. D'Agata EMC, Venkataraman L, DeGirolami P, et al: Colonization with broad-spectrum cephalosporin-resistant Gram-negative bacilli in intensive care units during a non-outbreak period: Prevalence, risk factors and rate of infection. *Crit Care Med* 1999; 27:1090–1095

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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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REFERENCES

1. Guidelines for Hand Hygiene in Health-Care Settings. Developed by the Healthcare Infection Control Practices Advisory Committee, the Society for Healthcare Epidemiology of America, the Association for Professionals in Infection Control and Epidemiology, and the Infectious Diseases Society of America. *MMWR Morb Mortal Wkly Rep* 2002; 51(RR16):1–44
2. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: Guidelines for the prevention of antimicrobial resistance in hospitals. *Clin Infect Dis* 1997; 25:584–599
3. Guidelines for the prevention of intravascular catheter-related infections. Developed by the Society of Critical Care Medicine, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, Surgical Infection Society, American College of Chest Physicians, American Thoracic Society, American Society of Critical Care Anesthesiologists,

Association for Professionals in Infection Control and Epidemiology, Infusion Nurses Society, Oncology Nursing Society, Society of Cardiovascular and Interventional Radiology, American Academy of Pediatrics, and the Centers for Disease Control and Prevention. *Clin Infect Dis* 2002; 35:1281–1307

DOI: 10.1097/01.CCM.0000153606.37258.74

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 healthcare 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.

Sebastian Schulz-Stubner, MD, PhD, University of Iowa College of Medicine, Iowa City, IA

REFERENCE

1. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873

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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 message." 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 restore consciousness, vigor, or life to" and second to "regain consciousness" (2). *Roget's II New Thesaurus*, 3rd edition, lists resuscitation as "the act of reviving or condition of being revived: reactivation, rebirth, renaissance, renascence, renewal, resurgence, resurrection, revitalization, 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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REFERENCES

1. *Stedman's Medical Dictionary*. 26th Edition. Baltimore, Williams & Wilkins, 1995
2. *The American Heritage College Dictionary*. 3rd Edition. Boston, Houghton Mifflin, 1997
3. *Roget's II The New Thesaurus*. 3rd Edition. Boston, Houghton Mifflin, 1995

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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 Kybersept study results.

The Kybersept 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.

Alain Eid, Pulmonary Associates, Colorado Springs, CO

REFERENCES

1. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
2. Warren BL, Eid A, Pillay SS, et al: Caring for the critically ill patient: High-dose antithrombin III in severe sepsis: A randomized controlled trial. *JAMA* 2001; 286:1869–1878
3. Taylor FB Jr, Emerson RE Jr, Jordan R, et al: Antithrombin-III prevents the lethal effects of *Escherichia coli* infusion in baboons. *Circ Shock* 1988; 26:227–235
4. Fourrier F, Chopin C, Huart JJ, et al: Double-blind, placebo-controlled trial of antithrombin III concentrates in septic shock with disseminated intravascular coagulation. *Chest* 1993; 104:882–888
5. Inthorn D, Hoffmann JN, Hartl WH, et al: Antithrombin III supplementation in severe sepsis: Beneficial effects on organ dysfunction. *Shock* 1997; 8:328–334

DOI: 10.1097/01.CCM.0000153591.98873.10

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. Eisele 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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REFERENCES

1. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
2. Warren BL, Eid A, Singer P, et al: High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; 286: 1869–1878
3. Bone RC, Balk RA, Fein AM, et al: A second large controlled clinical study of E5, a monoclonal antibody to endotoxin: results of a prospective, multicenter, randomized, controlled trial. *Crit Care Med* 1995; 23:994–1006

4. Opal SM, Fisher CJ, Dhainaut J-F, et al: Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. *Crit Care Med* 1997; 25:1115–1124
5. Reinhart K, Menger T, Gardlund B, et al: Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: the RAMSES study. *Crit Care Med* 2001; 29:765–769
6. Eisele B, Lamy M, Thijs LG, et al: Antithrombin III in patients with severe sepsis: a randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. *Intensive Care Med* 1998; 24:663–672

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Early or Late Tracheostomy

To the Editor:

We read with great interest the original article by Dr. Rumbak and colleagues (1), published in the August 2004 issue of *Critical Care Medicine*. Interestingly, in this study, mortality in the late tracheotomy group was surprisingly high. Indeed, actual mortality was well above the expected mortality (based on Acute Physiology and Chronic Health Evaluation [APACHE] II scores). Probably, high mortality was related to a high incidence of pneumonia in patients undergoing late tracheotomy, because in these patients, pneumonia was diagnosed five times more frequently than in patients undergoing early tracheotomy (25% vs 5%).

Importantly, patients were moved to stepdown facilities or ventilator floors while still undergoing mechanical ventilation, and the incidences of pneumonia may differ from one ward to another, depending on the measures taken to prevent pneumonia (2) or because of local outbreaks of infections. We suggest that such differences may have resulted in a difference in pneumonia in the two study groups. In other words, found differences may (also) have been caused by other factors than whether the patient received early or delayed tracheotomy.

More specifically, can the authors give answers to the following questions? At what time point did study patients develop pneumonia? Was it at the time they were still translaryngeally intubated or after tracheotomy? Where did patients develop pneumonia, on the ward where they were initially admitted or in subsequent departments? Finally, was there any difference between wards with respect to the incidences of pneumonia?

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REFERENCES

1. Rumbak MJ, Newton M, Truncale T, et al: A prospective, randomized study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. *Crit Care Med* 2004; 32:1689–1694
2. Kollef MH: Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. *Crit Care Med* 2004; 32:1396–1405

DOI: 10.1097/01.CCM.0000153586.99695.00

Further Clarification?

To the Editor:

I read with great interest the well-done study of Dr. Rumbak and colleagues (1), published in the August issue of *Critical Care Medicine*. However, some issues deserve further clarification because they are either very surprising or may be erroneous.

1. There are astonishingly many cases of overt disseminated intravascular coagulation in the two groups (see Table 1). Because the authors list exactly the same number of patients with high-dose vasopressor support, I wonder whether we are dealing with a simple typing error.
2. I do not want to bore either the authors or the readers, but I am of the opinion that for a scientific article, the language should be used in the most proper way possible: the term tracheotomy—originally deriving from the Greek word "tome" that means the cutting—describes a chirurgical technique that implies cutting the trachea. However, the technique used for this study and illustrated in the corresponding section was dilatational tracheostomy. As other authors (2, 3) do, I would have chosen the latter terminology. I am furthermore questioning which of the two terms (dilatational–dilational) would be the more appropriate, the former being the more frequently used (2, 5, and four other references cited in the article).
3. The patients from the interventional group underwent mechanical ventilation for only 7.6 days, although one of the four inclusion criteria was a projected need for ventilation of >14 days. So, we have to deal with a net reduction for ventilatory support of 9.8 days when compared with the delayed tracheostomy group. Are there any credible explanations for this result or was there eventually a bias in recruiting patients? Which phase of ventilatory support did primarily benefit from early tracheostomy: the phase of stabilization and (partial) healing or rather the weaning period? By intuition, one would rather opt for the latter. In fact, the authors list three possible reasons that concern above all weaning: less sedation, less work of breathing, as well as better lung mechanics. We know that difficult-to-wean patients actually can spend >40% of their whole intubation period being weaned (4). So, the dramatic decrease of ventilatory support from ≥14 days (projected) to 7.6 days (real) in the early tracheostomized group would, therefore, imply a virtually zero weaning period. Because this cannot be the case, we should look for other answers. I partially accept the author's attempt by mentioning a diminished cumulative incidence of ventilator-associated pneumonia in the early tracheostomy group (5% vs 25%), but I do not think it is sufficient as explication. Should we, therefore, assume that early tracheostomy also produces more rapid and better healing of the damaged lung, with consequently less associated organ failures, lower mortality, and shorter length of stay in the intensive care unit? This, of course, would be the most remarkable and even sensational result of this study, and I wonder whether the authors can comment on that.(5)

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REFERENCES

1. Rumbak MJ, Newton M, Truncale T, et al: A prospective, randomized study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. *Crit Care Med* 2004; 32:1689–1694
2. Ciaglia P, Firsching R, Syniec C: Elective percutaneous dilatational tracheostomy: A new simple bedside procedure: Preliminary report. *Chest* 1985; 87:715–719
3. Hazard PB, Garrett HE Jr, Adams JW, et al: