

## CORRESPONDENCE



## Corticosteroids for Septic Shock

**TO THE EDITOR:** On the basis of the Corticosteroid Therapy of Septic Shock (CORTICUS) study, Sprung et al. (Jan. 10 issue)<sup>1</sup> report that hydrocortisone does not improve survival among patients with septic shock. However, it is disturbing that of the 357 study patients with culture-positive sepsis, 86 (24%) were considered not to have received appropriate antimicrobial therapy. This was determined retrospectively by a clinical evaluation committee. The actual mortality rates among patients receiving appropriate antimicrobial therapy as compared with those receiving inappropriate antimicrobial therapy are not provided. Antimicrobial agents remain the cornerstone of therapy for sepsis.<sup>2</sup> However, this study shows that basic antimicrobial therapy continues to be clinically problematic in sepsis. A trial of septic shock in which one quarter of the culture-positive patients receive inappropriate antimicrobial therapy seems to defeat the hypothesized purpose of adjunctive corticosteroid use. It is unfortunate that the rec-

ommendations of the clinical evaluation committee regarding antimicrobial therapy were not available and were applied prospectively instead of retrospectively in this trial.

Mark R. Daley, B.Med.

Royal Prince Alfred Hospital  
Sydney 2050, Australia  
mark.daley@email.cs.nsw.gov.au

1. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008;358:111-24.
2. Bochud PY, Glauser MP, Calandra T. Antibiotics in sepsis. *Intensive Care Med* 2001;27:Suppl 1:S33-S48.

**TO THE EDITOR:** The failure of the CORTICUS study group to reach the enrollment target of 800 patients may have resulted from physician bias against enrolling more severely ill patients, given previously published data on the benefits of corticosteroids in septic shock.<sup>1-3</sup> The extent of this bias cannot be assessed, because the number of patients screened before randomization is not provided. The largest previous trial of low-dose corticosteroids for the treatment of septic shock enrolled patients in whom hypotension had persisted for 1 hour despite fluid resuscitation and vasopressor treatment.<sup>1</sup> In contrast, the CORTICUS study group enrolled patients who were not as severely ill, requiring only a systolic blood pressure of less than 90 mm Hg for 1 hour despite adequate fluid resuscitation or need for vasopressors.

The benefit of antiinflammatory agents in sepsis is directly proportional to the severity of illness.<sup>4</sup> The control-group mortality was 36% in the CORTICUS study, as compared with 63% in the study by Annane et al.<sup>1</sup> The lack of a treatment benefit in the CORTICUS study may be due to the enrollment of a population of patients with a

## THIS WEEK'S LETTERS

- 2068 Corticosteroids for Septic Shock
- 2071 Insulin and Pentastarch for Severe Sepsis
- 2075 Chimerism and Liver Transplantation
- 2076 More on Subgroup Analyses in Clinical Trials
- 2077 Dual Inheritance of Sudden Death from Cardiovascular Causes
- 2078 Augmentation of J Waves and Electrical Storms in Patients with Early Repolarization

lower mortality, for whom the risk of side effects of corticosteroid therapy outweighs its potential benefit.

Nitin Seam, M.D.

Veterans Affairs Medical Center  
Washington, DC 20422

1. Annane D, S ebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.
2. Minneci PC, Deans KJ, Banks SM, et al. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. *Ann Intern Med* 2004;141:47-56.
3. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ* 2004;329:480-8.
4. Eichacker PQ, Parent C, Kalil A, et al. Risk and efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. *Am J Respir Crit Care Med* 2002;166:1197-205.

**TO THE EDITOR:** Sprung et al. report the use of hydrocortisone at a physiologic dose to treat patients with septic shock. The study population was divided into two groups on the basis of their response to a 250- $\mu$ g corticotropin stimulation test. The absence of a response to corticotropin stimulation was defined as an increase in the serum cortisol level of less than 9  $\mu$ g per deciliter (248 nmol per liter). We have several points of concern. First, 24.8% of the nonresponders received etomidate, an anesthetic agent that also blocks the adrenal enzyme 11 $\beta$ -hydroxylase and cortisol synthesis.<sup>1</sup> We think that absolute cortisol levels and the cortisol area under the curve may be more precise ways to define adrenal insufficiency in septic shock.<sup>2,3</sup> In fact, basal cortisol levels were higher in the group without a response than in the group with a response. It is evident that the mean basal cortisol level was high in the nonresponders and that the standard deviation was very large. This suggests that the group was heterogeneous, clearly including not only patients with real adrenal insufficiency but also a sizable number of patients with normal cortisol secretion.

Rafael Luboshitzky, M.D.

Ghali Qupti, M.D.

Haemek Medical Center  
18101 Afula, Israel  
luboshitzky\_r@clalit.org.il

1. Jackson WL Jr. Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? A critical appraisal. *Chest* 2005;127:1031-8.
2. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. *Crit Care Med* 2003;31:141-5.
3. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. *J Clin Endocrinol Metab* 2006;91:3725-45.

**TO THE EDITOR:** Sprung et al. found no improvement in survival or shock reversal and an increase in superinfections. These conclusions contrast with those of a previous multicenter study<sup>1</sup> and of two meta-analyses<sup>2,3</sup> and should not lead to the abandonment of corticosteroids in this setting for several reasons. First, as emphasized in the accompanying editorial, the study was underpowered to detect an important effect of treatment on mortality. In addition, in a subgroup of patients whose illness was more severe than that in the entire study population, an absolute reduction in mortality of 11.2% was observed. Second, the rate of shock reversal at 28 days is less relevant than the rate observed earlier, since it underestimates what happens during the first days of treatment. Corticosteroids increase the pressor response to catecholamines,<sup>4</sup> which explains, at least in part, why a noticeable effect on shock reversal was observed on day 7 in all studies (including the current study reported by Sprung et al.). Third, since new episodes of sepsis and septic shock appeared to account for the increase in superinfections, we wonder how many episodes were confirmed by microbiologic assessment and how they were distinguished from possible shock rebound after corticosteroid treatment.

Pierre-Edouard Bollaert, M.D., Ph.D.

Nancy University Hospital  
54035 Nancy CEDEX, France  
pe.bollaert@chu-nancy.fr

1. Annane D, S ebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.
2. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ* 2004;329:480-8.
3. Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. *Ann Intern Med* 2004;141:47-56.
4. Bellissant E, Annane D. Effect of hydrocortisone on phenylephrine — mean arterial pressure dose-response relationship in septic shock. *Clin Pharmacol Ther* 2000;68:293-303.

**TO THE EDITOR:** We believe that selection bias confounds interpretation of the CORTICUS study findings for three reasons. First, the demographic characteristics of the enrolled patients differ from those of patients enrolled in the major sepsis trials of the past decade. Second, it appears that only 1 of 25 eligible patients was enrolled in the CORTICUS study.<sup>1</sup> Third, the study was terminated prematurely because of slow recruitment, which is odd, given that septic shock is the most com-

mon admission diagnosis in intensive care units (ICUs) worldwide.<sup>1</sup> The high prevalence of septic shock<sup>1</sup> and the overwhelming use of corticosteroids in its management<sup>2</sup> are critically disconnected from the stated inability to enroll patients in this study; this suggests that many of those screened — but not eligible — were ineligible because they were already receiving corticosteroids. We therefore believe that the fairest conclusion might be that corticosteroids were not likely to benefit patients with septic shock when their physicians had already decided that they were not sufficiently ill to warrant such therapy.

Paul E. Marik, M.D.

Thomas Jefferson University  
Philadelphia, PA 19107  
paul.marik@jefferson.edu

Stephen M. Pastores, M.D.

Memorial Sloan-Kettering Cancer Center  
New York, NY 10021

Brian P. Kavanagh, M.B.

Hospital for Sick Children  
Toronto, ON M5G 1X8, Canada

1. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;34:344-53.
2. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet* 2007;370:676-84. [Erratum, *Lancet* 2007;370:1034.]

**TO THE EDITOR:** Sprung et al. report that patients with septic shock who received etomidate had increased mortality. Etomidate decreases serum cortisol levels by inhibiting 11  $\beta$ -hydroxylase, and continuous etomidate infusions have been found to increase mortality among critically injured patients.<sup>1</sup> Retrospective studies of mortality and the use of single-dose etomidate in sepsis have yielded conflicting results,<sup>2,3</sup> and etomidate is less likely to cause hypotension and cardiac depression than other induction agents.<sup>3</sup> Although the assessment of hydrocortisone by Sprung et al. was prospective, their assessment of etomidate was not. Clinicians who are aware of etomidate's benign hemodynamic profile and potentially adverse metabolic effects may reserve it for patients who are most hemodynamically unstable at intubation. These patients may be more likely to die, regardless of treatment. In addition, it is notable that patients who received etomidate and hydrocortisone in the CORTICUS trial were at least as likely to die as pa-

tients who received etomidate but did not receive corticosteroid replacement. These considerations argue for a well-designed prospective trial of single-dose etomidate for intubation of patients with septic shock.

Seth Manoach, M.D.

SUNY Downstate Medical Center  
Brooklyn, NY 11203  
seth.manoach@downstate.edu

1. Watt I, Ledingham IM. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. *Anaesthesia* 1984; 39:973-81.
2. Lipiner-Friedman D, Sprung CL, Laterre PF, et al. Adrenal function in sepsis: the retrospective CORTICUS cohort study. *Crit Care Med* 2007;35:1012-8.
3. Ray DC, McKeown DW. Effect of induction agent of vasopressor and steroid use, and outcome in patients with septic shock. *Crit Care* 2007;11(3):R56.

**THE AUTHORS REPLY:** In response to Daley: 24% of patients were classified as not receiving appropriate antimicrobial therapy because of the strict criteria used by the clinical evaluation committee and frequent inability to confirm appropriateness. This included cases in which laboratory sensitivities were not reported for pathogens isolated or for the class of antibiotic used and cases in which prescribed antibiotics did not cover all of the multiple pathogens isolated. It is difficult to establish prospective antimicrobial guidelines since bacterial sensitivity patterns vary among ICUs and hospitals. A clinical evaluation committee is in the position of making retrospective analyses, when pathogens and sensitivity patterns are known. We believe that most of our patients did receive appropriate antibiotics, although some may have been classified as having received inappropriate antibiotics because of the lack of data. A higher mortality was seen among patients classified as receiving appropriate antimicrobial agents as compared with those not receiving appropriate antibiotics (35% vs. 23%).

We agree with Seam that the patients in the CORTICUS study were not as severely ill as those in the study by Annane et al.,<sup>1</sup> with lower mortality in the placebo group, lower scores on the Simplified Acute Physiology Score II, and fewer patients who did not have a response to corticotropin. Although corticosteroids may be effective if given early in a population of severely ill patients who do not have a response to vasopressor therapy,<sup>1</sup> the CORTICUS population represents patients who are more typical of those usually

seen. We appreciate Luboshitzky and Qupti's comments, but the definition and optimal diagnostic testing of adrenal insufficiency in septic shock remain controversial and elusive.

In response to Bollaert: although our study was underpowered, it is still, to our knowledge, the largest performed to date. Given that the relative risk of death was increased with corticosteroid use, the likelihood of a positive finding for hydrocortisone would have been low even if the targeted number of patients had been enrolled. It is important to assess subgroups that have been defined prospectively, since post hoc subgroup analyses can be misleading. The majority of patients with superinfections did not have new sepsis or septic shock. Among patients with new episodes of sepsis, microbiologic confirmation occurred in more than 50%. Although we acknowledge the difficulty in discriminating between rebound inflammation and new sepsis, repeat shock episodes in the hydrocortisone and placebo groups were similar.

In response to Marik et al., the patients in the CORTICUS study actually had 28-day and ICU mortality rates that were similar not only to those in the trial they cite but also to those in other contemporary trials involving patients with septic shock.<sup>2</sup> Consequently, our patients were sufficiently ill to warrant corticosteroid therapy. Sepsis is not septic shock. In the Sepsis Occurrence in Acutely Ill Patients (SOAP) study,<sup>3</sup> only 15% of patients had septic shock at some time during their ICU admission (7.7% on admission) and many would not have met our inclusion criteria. We acknowledge that we lack precise information for eligible patients who were not enrolled. The slow-

ness of recruitment was due in part to the many patients who were ineligible because they had already been given corticosteroids on the basis of recommendations for their use, but the study investigators had clinical equipoise for the use of corticosteroids in enrolled patients. As we noted, hydrocortisone use may benefit the small subgroup of patients with early, unresponsive septic shock. However, on the basis of currently available evidence, corticosteroids cannot be recommended for the majority of patients with septic shock who do have a response to vasopressors,<sup>4</sup> particularly in view of the increased risk of harmful complications.

Charles L. Sprung, M.D.

Hadassah Hebrew University Medical Center  
91120 Jerusalem, Israel  
sprung@cc.huji.ac.il

Mervyn Singer, M.D.

University College London  
London WC1E 6JJ, United Kingdom

Djillali Annane, M.D., Ph.D.

Raymond Poincaré Hospital  
(Assistance Publique—Hôpitaux de Paris)  
F-92380 Garches, France

for the CORTICUS Study Group

1. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.
2. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;358:877-87.
3. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;34:344-53.
4. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296-327.

## Insulin and Pentastarch for Severe Sepsis

**TO THE EDITOR:** Brunkhorst and colleagues (Jan. 10 issue)<sup>1</sup> report that the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study established “that intensive insulin therapy has no measurable, consistent benefit in critically ill patients” in a medical intensive care unit (ICU). This interpretation appears too conclusive, since the Supplementary Appendix of the article (available with the full text of the article at [www.nejm.org](http://www.nejm.org)) indicates that the goal of normoglycemia was reached in less than 50% of the patients in the intensive insulin-therapy group.

In addition to the intrinsic properties of an intensive insulin-therapy protocol, heterogeneity in the extrinsic factors (e.g., the level of training of nurses in the protocol and their workload) among centers participating in multicenter trials further influences the risk of failure to achieve normoglycemia.<sup>1,2</sup> The intensive-therapy protocol used by Brunkhorst et al. was previously used in two single-center trials, with a 70% rate of successful glycemic control.<sup>3-5</sup> To assess, in large multicenter trials, whether normoglycemia influences outcomes, the newly implemented protocol