EDITORIALS

Corticosteroids in Septic Shock

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As the balance of evidence regarding corticosteroid treatment for septic shock shifts once again toward the negative, the study by Sprung et al.[1] in this issue of the *Journal* elicits a strong feeling of déjà vu. Will the historical fate of high-dose corticosteroids, which were largely abandoned when the benefit observed in early studies could not be replicated in larger trials,[2,3] now befall "physiologic-dose" corticosteroids?

The rationale for therapy with corticosteroids at a physiologic dose (i.e., 200 to 300 mg of hydrocortisone per day) originated in the observations that patients with septic shock who had a reduced response to corticotropin (increase in total plasma cortisol, <9 μg per deciliter [248 nmol per liter]) were more likely to die[4] and that the pressor response to norepinephrine may be improved by the administration of hydrocortisone.[5] Although the validity of these observations appears to be increasingly doubtful as evidence accumulates that the standard corticotropin stimulation test is unreliable in critically ill patients,[6,7] the findings have led to interest in treating such patients with corticosteroids. Encouraging results in small trials[8,9] and then in a larger trial[10] led to current recommendations to treat patients with septic shock with physiologic doses of hydrocortisone.[11,12] The recommendations are based on five trials involving a total of 464 patients, of whom 265 (57.1%) died.[13] Even though various treatment regimens were used, all five trials reported fewer deaths in patients who received corticosteroids. A meta-analysis of these trials suggested that the use of corticosteroids reduced mortality.[13]

In the face of such evidence, why did Sprung et al. conduct the Corticosteroid Therapy of Septic Shock (CORTICUS) study? As noted by the authors, the current recommendations are heavily dependent on one trial conducted by Annane et al.[10] In that trial, patients were divided into "responders" and "nonresponders" on the basis of a corticotropin stimulation test; 229 of 299 patients (76.6%) did not have a response to corticotropin, a percentage that was much larger than the 40% the investigators expected. After statistical adjustment for baseline covariates, a significant reduction in the likelihood of death was observed in patients with no response to corticotropin who received corticosteroids. In contrast, crude estimates of in-hospital mortality were higher in patients who had a response to corticotropin.

Two additional features of this trial bear mentioning. First, patients who were assigned to receive hydrocortisone also received fludrocortisone, although the importance of this factor is unknown. Second, 24% of the patients received etomidate, a short-acting intravenous anesthetic agent that selectively inhibits adrenal corticosteroid synthesis. Its use may have contributed to the unexpectedly high number of patients who did not have a response to corticotropin, and whether the trial results apply in health care systems in which etomidate is rarely used is unclear. Thus, the borderline result that was achieved only after statistical adjustment (combined with the unexpectedly high number of patients who did not have a response to corticotropin and the higher estimated mortality in those who did have a response to corticotropin) provide ample justification for the CORTICUS study.

Patients who were enrolled in the CORTICUS study had septic shock and remained hypotensive or required treatment with vasopressors for at least 1 hour after adequate fluid resuscitation.

Initially, patients were required to undergo randomization within 24 hours after the onset of septic shock; this time window was subsequently increased to 72 hours. Patients received either 200 mg of hydrocortisone per day or placebo for 5 days; they then received a tapered dose of hydrocortisone during the next 6 days, after which time the drug was stopped. The primary end point was death from any cause at 28 days in patients who did not have a response to corticotropin. Because of slow recruitment and expiry of the supply of study drug, the trial was stopped after only 500 of the planned 800 patients had been recruited. Before treatment, patients underwent a corticotropin stimulation test, in which 46.7% did not have a response.

The two study groups were well matched at baseline. Of 499 patients, 384 (77.0%) started study treatment within 12 hours after the onset of septic shock, and all but 6 patients were receiving inotropic agents or vasopressors at the time of enrollment; 87% of patients in each study group received at least 90% of their assigned study drug. The use of open-label corticosteroids and other reported concomitant treatments was similar in the two groups, and 19.2% of the patients received etomidate before enrollment.

The rate of death in the control group was lower than expected, and this factor, combined with early stopping of the study, meant that the study had a power of less than 35% to detect a 20% reduction in the relative risk of death. With this caveat, the primary conclusion of the study was that treatment with corticosteroids had no effect on the rate of death at 28 days, a finding that was consistent in the overall population (relative risk, 1.09; 95% confidence interval [CI], 0.84 to 1.41), in patients who had a response to corticotropin (relative risk, 1.00; 95% CI, 0.68 to 1.49), and in those who did not have a response to corticotropin (relative risk, 1.09; 95% CI, 0.77 to 1.52). The lack of treatment effect was also consistent regardless of the duration of septic shock before recruitment. Also notable is that shock was reversed more rapidly in patients receiving hydrocortisone but that this factor did not result in reduced mortality.

What, then, are the take-home messages for clinicians, researchers, and policymakers? To date, the CORTICUS study is the largest trial of corticosteroids in patients with septic shock but was still inadequately powered to detect a clinically important treatment effect. The 95% confidence interval for the relative risk of death (0.84 to 1.41) includes the overall point estimate from the study by Annane (0.89); therefore, the results of the two studies are not inconsistent. A meta-analysis that includes data from the CORTICUS trial is not likely to support the use of corticosteroids, and it seems clear that the corticotropin stimulation test does not identify patients who would benefit from corticosteroids. Clinicians who treat their patients with corticosteroids because they have observed a rapid reduction in the need for vasopressors should be aware that more rapid weaning from vasopressors is an unreliable surrogate outcome since it does not predict improved survival.

To researchers it should be clear that substantial uncertainty over the role of corticosteroids persists. Reliable treatment recommendations will be possible only if a much larger trial is conducted. To avoid generating further uncertainty, the minimum sample size should substantially exceed the total number of patients who have been studied so far. The detection of a 15% reduction in relative risk from a rate of death of 35% will require a study of at least 2600 patients. Although such a number is daunting, the advent of trials consortia for critical care may make such a study possible.[14]

Promulgation of evidence-based guidelines is an advance welcomed by many clinicians, although treatment recommendations are inevitably constrained by the quality of the available evidence. Those writing or promoting treatment guidelines should recognize that firm recommendations based on small trials or meta-analyses may be misleading because of random error, and the inclusion of older trials with methodologic limitations may introduce systematic error.[15] Furthermore, the CORTICUS investigators stated that it was likely that current guidelines inhibited recruitment to their trial; in some situations, apparently authoritative guidelines may make the conduct of important confirmatory trials more difficult.

Although the CORTICUS study was unable to define the role of corticosteroids in septic shock, the investigators performed a valuable service. They reminded us that few critical care practices or treatment recommendations are based on unequivocal evidence and that, in some instances, critical appraisal and an open mind may be more

appropriate than unquestioning adherence to guidelines. Perhaps the greatest service we can do our patients is to conduct the large, high-quality trials needed to base our clinical practice on truly robust evidence.

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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. The Veterans Administration Systemic Sepsis Cooperative Study Group. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 1987;317:659-65.
3. Bone RC, Fisher CJ Jr, Clemmer TP, et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987;317:653-8.
4. Rothwell PM, Udwadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. Lancet 1991;337:582-3.
5. Annane D, Bellissant E, Sebille V, et al. Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. Br J Clin Pharmacol 1998;46:589-97.
6. Rai R, Cohen J, Venkatesh B. Assessment of adrenocortical function in the critically ill. Crit Care Resusc 2004;6:123-9.
7. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. N Engl J Med 2004;350:1629-38.
8. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 1998;26:645-50.
9. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med 1999;27:723-32.
10. 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.
11. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858-73. [Errata, Crit Care Med 2004;32:1448, 2169-70.]
12. 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.
13. 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.
14. Cook DJ, Brower R, Cooper J, Brochard L, Vincent JL. Multicenter clinical research in adult critical care. Crit Care Med 2002;30:1636-43.
15. Graf J, Doig GS, Cook DJ, Vincent JL, Sibbald WJ. Randomized, controlled clinical trials in sepsis: has methodological quality improved over time? Crit Care Med 2002;30:461-72.

Efficacy of Sirolimus in Treating Tuberous Sclerosis and Lymphangioleiomyomatosis

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Owing to their immunosuppressive and antiproliferative effects, sirolimus (also called rapamycin) and related drugs are being evaluated as part of many transplant immunosuppresion regimens, as well as for a plethora of medical conditions such as type 1 diabetes, macular degeneration, coronary artery disease, and metastatic or refractory cancers of the breast, prostate, lung, and liver, to name but a few.

The effects of sirolimus are mediated by its inhibition of the curiously named cytoplasmic protein mammalian target of rapamycin (mTOR), a ubiquitous serine–threonine kinase that is intimately involved in the regulation of protein synthesis, cell growth, cytoskeletal organization, and other features of cellular homeostasis. Insulin, growth factors, and amino acids are a few of the extracellular stimuli that increase mTOR activity, whereas hypoxia, dehydration, and depletion of ATP or amino acids seem to inhibit its function (for reviews, see Corradetti and Guan[1] and Wang and Proud[2]).

In this issue of the *Journal*, Bissler et al. report on their prospective clinical trial of sirolimus therapy in patients with the tuberous sclerosis complex, lymphangioleiomyomatosis, or both.[3] The tuberous sclerosis complex is a genetic syndrome characterized, in part, by sporadic tumorigenesis in multiorgan systems. The tuberous sclerosis complex is caused by inactivating genetic mutations of the *TSC1* or *TSC2* tumor-suppressor genes. Normally, the cytoplasmic TSC1 and TSC2 proteins (also called hamartin and tuberin, respectively) interact and inhibit mTOR activity. In the absence of a normally functioning TSC1–TSC2 complex, mTOR activity increases, and tumors grow in various organ systems including the kidney, lung, brain, and skin (for a review, see Crino et al.[4]). The recent explosion of molecular-genetic discoveries and elucidation of signaling pathways involved in cell growth suggest that a drug that inhibits mTOR might be therapeutic in patients with the tuberous sclerosis complex.