Commentary

Pro/con clinical debate: Are steroids useful in the management of patients with septic shock?

Frank V Ritacca*, Carmine Simone†‡, Randy Wax§¶, Katherine G Craig** and Keith R Walley††

*Resident, Department of Medicine, University of Toronto, Canada
†Resident, Division of Thoracic Surgery, University of Toronto, Canada
‡Resident, Division of Critical Care Medicine, Mount Sinai Hospital, Toronto, Canada
§Lecturer, Department of Medicine, University of Toronto, Canada
¶Staff Intensivist, Division of Critical Care Medicine, Mount Sinai Hospital, Toronto, Canada
**Fellow in Critical Care Medicine, Division of Critical Care, University of British Columbia, Vancouver, Canada
††Professor of Medicine, Division of Critical Care, University of British Columbia, Vancouver, Canada

Correspondence: *Critical Care Forum* Editorial Office, editorial@ccforum.com

Published online: 6 February 2002 *Critical Care* 2002, **6**:113-116

Abstract

Decision-making in the intensive care unit is often very difficult. Although we are encouraged to make evidence-based decisions, this may be difficult for a number of reasons. To begin with, evidence may not exist to answer the clinical question. Second, when there is evidence it may not be applicable to the patient in question or the clinician may be reluctant to apply it to the patient based on a number of secondary issues such as costs, premorbid condition or possible complications. Finally, emotions are often highly charged when caring for patients that have a significant chance of death, and care-givers as well as families are frequently prepared to take chances on a therapy whose benefit is not entirely clear. Steroid use in septic shock is an example of a therapy that makes some sense but has conflicting support in the literature. In this issue of *Critical Care Forum*, the two sides of this often heated debate are brought to the forefront in an interesting format.

Keywords glucocorticoids, sepsis, shock

The scenario

A 60-year-old man has been in your intensive care unit with septic shock for 5 days and he has required a norepinephrine infusion for the entire time. He had multisystem organ failure but most of the organs have improved. He has good urine output and does not have any evidence of heart failure. There is no active bleeding and currently no signs of new or ongoing infection. You wonder whether steroids might help facilitate his recovery.

Pro: steroids are useful in the management of septic shock

Frank V Ritacca, Carmine Simone and Randy Wax

Despite advances in providing care for patients with septic shock, mortality rates remain unacceptably high. Exogenous corticosteroids have potent anti-inflammatory effects and their use for modulation of the host response in septic shock has been debated for decades. Two meta-analyses have suggested that high-dose steroids are not beneficial in patients with septic shock [1,2]. These results should not be generalized to treatment with low-dose corticosteroids. We believe there are recent data showing that low-dose corticosteroids hasten discontinuation of vasopressors in refractory septic shock, and may improve outcome.

ACTH = adrenocorticotrophic hormone.

Table 1

Summary of prospective studies suggesting benefit for use of corticosteroids in patients with septic shock

Study	Design	Therapy	Outcome
Bollaert *et al*. [7]	Prospective, randomized, double-blind, placebo-controlled trial	100 mg hydrocortisone intravenously every 8 h for 5 days	Shock reversal at 7 days; treatment, 68% (15/22); placebo, 21% (4/19). $P = 0.007$
Briegel *et al*. [8]	Prospective, randomized, double-blind, placebo-controlled trial	100 mg hydrocortisone intravenous loading dose plus infusion at 0.18 mg/kg/h until shock reversal, then wean infusion	Median time to cessation of vasopressor support; treatment ($n = 20$), 2 days versus placebo ($n = 20$), 7 days. $P = 0.005$
Annane [9]	Prospective, randomized, double-blind, placebo-controlled trial	50 mg hydrocortisone intravenously every 5 h + 50 μg fludrocortisone perorally once daily for 7 days	28-day survival by Cox model, 28.8% relative risk reduction for treatment ($n = 150$) versus placebo ($n = 149$). Relative risk, 0.712; 95% confidence interval, 0.525–0.965

Demonstration of an intact hypothalamic–pituitary–adrenal axis response has been associated with reduced mortality in septic shock [3]. Corticosteroids can regulate the synthesis and function of catecholamines and their receptors, which in turn control vascular tone and organ perfusion [4]. Proinflammatory cytokines released in sepsis alter steroid responsiveness, leading to the deleterious effects of catecholamine dysfunction and refractory hypotension [5]. Downregulation of catecholamine receptors occurs with prolonged use of exogenous catecholamines and this may be reversed with administration of low-dose steroids [6]. Restoring endogenous regulation of vasomotor tone would be desirable to preserve regional regulation of perfusion.

Three recent clinical trials have provided encouraging results for the use of corticosteroids in septic shock (Table 1). Patients were treated with corticosteroids at lower doses and for a longer interval than in previous trials. Bollaert *et al*. showed that patients receiving low-dose steroids had a significantly higher rate of shock reversal (stable blood pressure without fluid boluses or vasopressors) [7]. The treatment effect was present irrespective of hypothalamic–pituitary–adrenal axis function as measured by an adrenocorticotrophic hormone (ACTH) stimulation test.

Briegel *et al*. similarly found that low-dose corticosteroids could hasten independence from vasopressor support [8]. There were no trends suggesting treatment-related adverse events in either trial. Although no mortality benefits were found, increased rates of shock reversal may imply decreased resource use (e.g. shorter length of stay in the intensive care unit) and complications (e.g. catheter-related infections).

Data published in abstract form from a multicenter trial testing low-dose corticosteroid and mineralocorticoid support led to a relative risk reduction of almost 30% in patients with septic shock [9]. The survival benefit of combination therapy was significant only in patients with blunted response to ACTH stimulation. However, this may be due to a smaller number of patients in the normal response group.

Finally, one retrospective study suggests that low-dose corticosteroids may reduce post-traumatic stress disorder and improve health-related quality of life in survivors of septic shock [10].

Although exciting developments in targeted drug therapy for sepsis have occurred recently, supportive care remains key to maximizing survival in patients. We view appropriate supplementation of corticosteroids as part of the regimen of supportive care. Even if subsequent studies do not confirm a mortality reduction, 'fewer days of vasopressor dependence' may itself be an important outcome. Given that the patient described for this debate appears to have been adequately treated for infection, repair of sepsis-induced dysregulation of vasomotor tone using low-dose corticosteroids is reasonable and appropriate.

Con: steroids are not useful in the management of septic shock

Katherine G Craig and Keith R Walley

The debate surrounding the use of corticosteroids in septic patients has continued for over 30 years. Two meta-analyses in the mid-1990s seemed to put an end to the controversy. The conclusions drawn from these works were that corticosteroids provided no benefit to patients with septic shock [2] and that corticosteroids may actually cause harm, as evidenced by a slight increase in overall mortality [1].

The debate has recently been re-opened by several small, prospective, randomized, placebo-controlled trials. A study by Bollaert *et al*., in which septic patients requiring catecholamines were randomized to receive hydrocortisone (100 mg intravenously three times a day for 5 days) or placebo, found a significant reduction in the time it took to reverse shock, and a trend towards improved survival [7]. While the results of this trial were impressive, care must be taken not to overinterpret the results; it was a small clinical trial with only about 20 patients in each arm, and there was a relatively high mortality rate in the placebo arm (63%) for patients with septic shock [11].

In a similar small trial by Briegel *et al*., septic shock patients were randomized to receive either a placebo or hydrocortisone (100 mg intravenous bolus), followed by continuous infusion until septic shock resolved [8]. The length of time for which vasopressor support was required was significantly reduced, and measures such as mean arterial pressure and systemic vascular resistance index were increased in patients treated with steroids. In addition, there were trends toward earlier reversal of organ dysfunction. There was not, however, a mortality difference between the two groups [8].

It may be germane to recognize that all benefit of immunomodulatory therapy in adequately powered, randomized, controlled trials is confined to the most severely ill [12–15]. This does not fit with the patient described in the aforementioned scenario.

Clinical case

In view of conflicting older, yet strong, evidence (that high-dose steroids are not beneficial) and newer, yet preliminary, studies (that suggest low-dose steroids are beneficial), the question becomes one of whether steroid-induced reversal of vasopressor support confers any outcome benefits. Unfortunately, no definitive work has been published.

The patient described in the present scenario is improving in all aspects of organ failure, but remains catecholamine dependent. A thorough examination and review of his management needs to be conducted to ensure no reversible cause of hypotension can be determined. A corticotropin stimulation test should be performed and absolute adrenal insufficiency should be treated.

There is ongoing debate in the literature as to the usefulness of this corticotropin stimulation test in so-called 'relative adrenal insufficient' patients, although it may be of prognostic significance [16]. A recent study by Schroeder *et al*. found low basal plasma cortisol levels and diminished responses to corticotropin-releasing hormone in patients that died of septic shock as compared with those who survived [17]. Annane *et al*., however, found an elevated basal cortisol level ($\geq$34 μg/dl) and a poor response to corticotropin (e.g. $\leq$9 μg/dl elevation at 30 or 60 min) to be a predictor of the poorest survival in patients with sepsis [3].

At this point in time there is not sufficient evidence to guide clinical practice. We therefore do not advocate use of steroids in this clinically improving patient without another indication. We must be cautious in our enthusiasm to try new therapies as history provides many examples of promising small clinical trials that have not held up to the test of time and larger, multicentered trials.

Pro's response

Frank V Ritacca, Carmine Simone and Randy Wax

Applying data from trials using high-dose steroids is inappropriate and leads to therapeutic nihilism. Life-saving therapy, such as low-dose beta-blockers in severe cardiomyopathy, met similar resistance because of poor experiences with identical drugs given in higher doses [18].

Levels of cortisol and responsiveness to ACTH stimulation in patients with sepsis vary considerably [19–21]. A normal corticotropin stimulation test result cannot exclude benefit of low-dose corticosteroids [7,22]. Although this patient is not 'most severely ill', catecholamine receptor effects may be more important than the immunomodulatory effects of this therapy [22]. This patient remains a candidate for low-dose corticosteroids.

Con's response

Katherine G Craig and Keith R Walley

While the foundations of the pro/con debates are remarkably similar, the resulting recommendations are not. Dr Ritacca and colleagues suggest that "appropriate supplementation of corticosteroids [be] part of the regimen of supportive care". There are several problems with this statement. First, with the level of evidence currently available it must be recognized that the use of steroids in sepsis, while promising, is still experimental, and should not be given the same status as routine measures of supportive care. Second, even if a physician makes a conscious decision to try steroids, there are again no data to suggest a dose or timing for 'appropriate supplementation'.

Much work remains to be carried out in this field. We urge restraint and recognition of the potential adverse side effects of, and lack of clear evidence for, steroid therapy in sepsis.

References

1. Cronin L, Cook DJ, Carlet J, Heyland DK, King D, Lansang MA, Fisher CJ Jr: **Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature**. *Crit Care Med* 1995, **23**:1430-1439.
2. Lefering R, Neugebauer EAM: **Steroid controversy in sepsis and septic shock: a meta-analysis**. *Crit Care Med* 1995, **23**: 1294-1303.
3. Annane D, Sébille V, Troché G, Raphaël J, Gajdos P, Bellissant E: **A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin**. *JAMA* 2000, **283**:1038-1045.
4. Barnes PJ, Adcock IM: **Glucocorticoid receptors**. In *The Lung: Scientific Foundations*. Edited by West JB, Barnes PJ, Weibel ER, Crystal RG. Philadelphia: Lippincott-Raven Publishers; 1997: 37-55.
5. Chrousos GP: **The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation**. *N Engl J Med* 1995, **332**: 1351-1362.
6. Barnes P: **Beta-adrenergic receptors and their regulation**. *Am J Respir Crit Care Med* 1995, **152**:838-860.
7. 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**:645-650.
8. Briegel J, Forst H, Schelling G, Kilger E, Kuprat G, Hemmer B, Hummel T, Lenhart A, Heyduck M, Stoll C, Peter K: **Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single center study**. *Crit Care Med* 1999, **27**:723-732.
9. Annane D: **Effects of the combination of hydrocortisone (HC)–fludro-cortisone (FC) on mortality in septic shock [abstract]**. *Crit Care Med* 2000, **28**:A63.
10. Schelling G, Stoll C, Kapfhammer HP, Rothenhausler HB, Krauseneck T, Durst K, Haller M, Briegel J: **The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder and health-related quality of life in survivors.** *Crit Care Med* 1999, **27**:2678-2683.
11. Balk RA: **Severe sepsis and septic shock: definitions, epidemiology, and clinical manifestations.** *Crit Care Clin* 2000, **16**:179-192.
12. Fisher CJ, Dhainaut JFA, Opal SM, Pribble JP, Balk RA, Slotman GJ, Iberti TJ, Rackow EC, Shapiro MJ, Greenman RL, Reines D, Shelly MP, Thompson BW, LaBrecque JF, Catalano MA, Knaus WA, Sadoff JC: **Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome: results from a randomized, double-blind, placebo-controlled trial.** *JAMA* 1994, **271**:1836-1843.
13. Abraham E, Wunderlink R, Silverman H, Perl TM, Nasraway S, Levy H, Bone R, Wenzel RP, Balk R, Allred R, Pennington JE, Wherry JC: **Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome: a randomized, controlled, double-blind, multicenter clinical trial.** *JAMA* 1995, **273**: 934-941.
14. Ziegler EJ, Fisher CJ, Sprung CL, Straube RC, Sadoff JC, Foulke GE, Wortel CH, Fink MP, Dellinger RP, Teng NN for the HA-1A sepsis study group: **Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: a randomized, double-blind, placebo-controlled trial.** *N Engl J Med* 1991, **324**:429-436.
15. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ: **Efficacy and safety of recombinant human activated protein C for severe sepsis.** *N Engl J Med* 2001, **344**: 699-709.
16. Lamberts SWJ, Bruining HA, de Jong FH: **Corticosteroid therapy in severe illness.** *N Engl J Med* 1997, **337**:1285-1292.
17. Schroeder S, Wichers M, Klingmüller D, Höfer M, Lehmann LE, von Spiegel T, Hering R, Putensen C, Hoeft A, Stüber F: **The hypothalamic–pituitary–adrenal axis of patients with severe sepsis: altered response to corticotropin-releasing hormone.** *Crit Care Med* 2001, **29**:310-316.
18. Califf RM, O'Connor CM: **Beta-blocker therapy for heart failure: the evidence is in, now the work begins.** *JAMA* 2000; **283**: 1335-1337.
19. Jurney TH, Cockrell JL, Lindberg JS, Lamiell JM, Wade CE: **Spectrum of cortisol and response to ACTH in ICU patients**. *Chest* 1987, **92**:292-295.
20. Drucker D, Shandling M: **Variable adrenocortical function in acute medical illness**. *Crit Care Med* 1985, **13**:477-479.
21. Sibbald WJ, Short A, Cohen M, Wilson RF: **Variations in adrenocortical responsiveness during severe bacterial infections**. *Ann Surg* 1977, **186**:29-33.
22. Matot I, Sprung CL: **Corticosteroids in septic shock: resurrection of the last rites**. *Crit Care Med* 1998, **26**:627-630.