

Commentary

The International Sepsis Forum's controversies in sepsis: corticosteroids should not be routinely used to treat septic shock

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Abstract

Corticosteroid treatment of severe sepsis has been one of the most controversial clinical issues in critical care. In fact, few agents can claim to have been evaluated in scores of studies spanning 3–4 decades. Yet, convincing proof that corticosteroids are useful pharmacologic agents in the treatment of this major clinical problem remains elusive. Recently, interest has resurfaced but this time the focus is on a steroid replacement approach for what has now been termed "relative adrenal insufficiency" rather than relying on the pharmacologic effects of steroids. This route holds promise, but proof remains lacking.

Keywords corticosteroids, septic shock

The issue of whether to use corticosteroids for treating septic shock has been ongoing for 20 or 30 years. Indeed, there is much clinical and preclinical data that provide ample reasons for using corticosteroids in septic shock. For instance, we know that steroids increase catecholamine-stimulated contractility, vasomotor catecholamine response, and adrenergic receptor density. They also prevent desensitization of β receptors, and they may provide adrenal replacement.

Cortisol status

The normal cortisol range is 5–24 $\mu\text{g}/\text{dl}$, and during the stress response this rarely goes above 200 $\mu\text{g}/\text{dl}$. During septic shock, classic adrenal insufficiency is rare (0–3% of cases) and cortisol levels can range from 7 to 400 $\mu\text{g}/\text{dl}$. However, 50% of patients have levels below 20 $\mu\text{g}/\text{dl}$ [1]. A series of studies has examined the relative adrenal insufficiency that is sometimes seen in septic shock. In one such study [2] patients were stimulated with adrenocorticotrophic hormone (ACTH) and their blood cortisol levels were measured at 0, 30, and 60 min. High mortality (82%) was associated with high baseline cortisol levels that did not respond to ACTH stimulation, whereas low mortality (26%) was associated with

low baseline cortisol levels that did respond to ACTH stimulation. The intermediate values correlated with intermediate mortality. This makes perfect sense and is very logical, which is one of the reasons why I think it has been adopted so quickly even though the data are fairly preliminary and have not been reproduced.

A recent study examined a cohort of patients with septic shock, separated them according to the presence or absence of relative adrenal insufficiency, randomized them into a placebo-controlled trial of steroid therapy, and then stratified the analysis according to the adrenal insufficiency variable [3]. At the onset, patients were tested for eligibility using ACTH stimulation (although the results of this were not immediately disclosed) and were then randomly assigned to either hydrocortisone plus a fluorinated steroid or placebo for 7 days, in other words adrenal replacement therapy versus none. The authors found that the group with relative adrenal insufficiency (by the new criteria) were observed to have statistically significantly improved survival. This tells us that there is a select population of patients with adrenal insufficiency during septic shock who improve when treated

with steroids. In spite of the fact that the responders (to ACTH) did not show a benefit, steroids worked in the group as a whole. Hence, that categorization did not actually matter. The 'take home message' ought to be that steroids work in septic shock based on the overall study result in all enrolled patients on an intent-to-treat basis. The sticky part is that this population has been studied with steroids many times in the past but without success.

Predicting outcome

So, do cortisol levels predict outcome? Several studies have looked at this: five studies found that nonsurvivors have higher levels of cortisol [4–8]; one found that survivors have higher levels [9]; and three found no correlation [10–12]. Therefore, these reports taken together indicate that cortisol levels do not predict outcome.

Does response to ACTH predict outcome? Two studies [11,13] found no correlation with outcome, whereas two other studies [10,14] found that a small (inadequate?) response predicts death. Therefore, as yet there is not enough evidence to state that response to ACTH is a critically important determinant of outcome. Moreover, in those studies, as well as in others, cortisol response is poorly reproducible, even on the same day and in the same patient [13,15]. Thus, even if response to ACTH were a good measure, it is hard to get reliable clinical data.

So what do we truly know about cortisol assessment in the intensive care unit? We know that appropriate levels are not yet known, low random values are difficult to interpret, and the concept of relative adrenal insufficiency is still poorly established. Thus, why not study all comers in septic shock, ignoring whether the patient is adrenally insufficient or not? A couple of studies have addressed this.

A study by Briegel and colleagues [16] was a double-blind, randomized trial of 40 patients that used the duration of vasopressor therapy as the end-point. The inclusion criterion was patients on vasopressor therapy with a cardiac index greater than 4, in other words those with vasodilated shock. The treatment was 100 mg hydrocortisone over the first 30 min, and then 0.18 mg/kg per hour for as long as the vasopressor was required. For shock reversal there was no significant difference from the control group; the median time on vasopressor was different (but it is not clear what this means because shock reversal showed no difference); and the mortality was identical.

In another randomized double-blind study (this time in 41 patients with septic shock requiring vasopressors for more than 48 hours) [17], the end-points were shock reversal, haemodynamics, and survival. Hydrocortisone 100 mg was given every 8 hours for 5 days, versus placebo. There was a statistically significant increase in the number of patients whose shock had reversed by day 7, and there was

a trend toward increased survival, although the numbers were small (6 deaths out of 22 in the corticosteroid group and 13 out of 19 in the control group).

Based on those two studies [16,17], the ACTH response does not appear to be necessary to see the shock effect. One interpretation of these data would be that stress steroids was the right approach, whereas high-dose pulse steroid therapy in all patients (not just adrenal insufficient patients) with septic shock was the wrong approach. Some have stated that steroids might have worked if they had been administered in a less potent way, for instance 100–300 mg/day over several days rather than the high doses given in earlier studies, suggesting that replacement of stress levels is what is important. However, this may not be the case (see below).

Treating shock versus mortality

This brings us to the study conducted by Sprung and colleagues of high-dose hydrocorticosteroids in septic shock [18]. Here the end-points were survival and reversal of shock. It was a randomized, prospective trial of 59 patients with septic shock and systolic blood pressure below 90 mmHg after adequate fluids. Treatment was industrial strength methylprednisolone 30 mg/kg or dexamethasone 6 mg/kg, and if shock persisted the dose was repeated after 4 hours to a maximum of two doses (i.e. very short pulse therapy). Shock reversal occurred more rapidly in the corticosteroid-treated patients than in the control group, and this lasted until day 14. There was no difference in mortality between the control group and the corticosteroid group at 25 days. Therefore, shock was actually improved more rapidly with treatment but mortality was no different. There may have been some late steroid deaths that were related to treatment.

What do we do now? One or two pulses of very high-dose steroids is effective in reversing shock, but with a conflicting effect on mortality. In summary, the pathophysiologic basis for using steroids in septic shock remains very confusing; the field is plagued by a large number of small trials and there is no doubt that steroids carry risk. Thus, if we do not know that something works, then we should not be using it. A large randomized trial is really needed here to answer this question. We do not know who to treat, we do not know when to treat, we do not know the dose to use, and we certainly do not know for how long to maintain treatment.

Finally, in a meta-analysis of all major studies conducted since 1963 [19] it was shown that the relative risk for death with corticosteroid treatment is slightly increased; in other words, there is a slight increased risk for death associated with corticosteroids. Therefore, the challenge is for us to come up with a study design that can give us a clear idea of what we should be doing in our everyday practice. For now, the data indicate that we should not administer steroids to patients who are in shock.

Competing interests

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References

1. Matot I, Sprung CL: **Corticosteroids in septic shock: resurrection of the last rites?** *Crit Care Med* 1998, **26**:627-630.
2. Annane D, Sebille V, Troche G, Raphael JC, 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.
3. Annane D: **Effects of the combination of hydrocortisone-fludrocortisone on mortality in septic shock.** *Crit Care Med* 2000, **28 (suppl)**:63.
4. Jurney TH, Cockrell JL Jr, Lindberg JS, Lamiell JM, Wade CE: **Spectrum of serum cortisol response to ACTH in ICU patients. Correlation with degree of illness and mortality.** *Chest* 1987, **92**:292-295.
5. Span LF, Hermus AR, Bartelink AK, Hoitsma AJ, Gimbrere JS, Smals AG, Kloppenborg PW: **Adrenocortical function: an indicator of severity of disease and survival in chronic critically ill patients.** *Intensive Care Med* 1992, **18**:93-96.
6. Jarek MJ, Legare EJ, McDermott MT, Merenich JA, Kollef MH: **Endocrine profiles for outcome prediction from the intensive care unit.** *Crit Care Med* 1993, **21**:543-550.
7. Drucker D, Shandling M: **Variable adrenocortical function in acute medical illness.** *Crit Care Med* 1985, **13**:477-479.
8. Rothwell PM, Lawler PG: **Prediction of outcome in intensive care patients using endocrine parameters.** *Crit Care Med* 1995, **23**:78-83.
9. McKee JI, Finlay WEI: **Cortisol replacement in severely stressed patients.** *Lancet* 1983; **i**:484.
10. Rothwell PM, Udwalla ZF, Lawler PG: **Cortisol response to corticotropin and survival in septic shock.** *Lancet* 1991, **337**:582-583.
11. Bouachour G, Tirot P, Gouello JP, Mathieu E, Vincent JF, Alquier P: **Adrenocortical function during septic shock.** *Intensive Care Med* 1995, **21**:57-62.
12. Schein RM, Sprung CL, Marcial E, Napolitano L, Chernow B: **Plasma cortisol levels in patients with septic shock.** *Crit Care Med* 1990, **18**:259-263.
13. Bouachour G, Roy PM, Guiraud MP: **The repetitive short corticotropin stimulation test in patients with septic shock.** *Ann Intern Med* 1995, **123**:962-963.
14. Moran JL, Chapman MJ, O'Fathartaigh MS, Peisach AR, Pannall PR, Leppard P: **Hypocortisolaemia and adrenocortical responsiveness and onset of septic shock.** *Intensive Care Med* 1994, **20**:489-495.
15. May ME, Carey RM: **Rapid adrenocorticotrophic hormone test in practice.** *Am J Med* 1985, **79**:679-684.
16. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, Hemmer B, Hummel T, Lenhart A, Heyduck M, Stoll C, Peter K: **Stress doses of hyperdynamic septic shock: a prospective, randomized, double-blind, single center study.** *Crit Care Med* 1999, **27**:723-732.
17. 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.
18. Sprung CL, Caralis PV, Marcial EH, Pierce M, Gelbard MA, Long WM, Duncan RC, Tendler MD, Karpf M: **The effect of high-dose corticosteroids in patients with septic shock: a prospective, controlled study.** *N Engl J Med* 1984, **311**:1137-1143.
19. Cronin L, Cook DJ, Carlet J, Heyland DK, King DBM, Lansang MAD, Fisher Jr CJ: **Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature.** *Crit Care Med* 1995, **23**:1430-1439.