Review

Pro-Con Debate: Steroid use in ACTH non-responsive septic shock patients with high baseline cortisol levels

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Abstract

Steroid use in critically ill, vasopressor-dependant, septic patients has gained increased acceptance in recent years with the publication of encouraging data. However, with renewed interest and/or attention comes increased debate and analysis. As a result, it is not surprising to find that there is still significant controversy with regards to the role of steroids in many patients. In this article, two expert groups debate the role of steroid use in a septic shock patient with arguably no clear evidence of adrenal insufficiency.

The scenario

A 57-year-old female has been admitted to the intensive care unit for 24 hours with septic shock. The patient requires significant amounts of noradrenaline (norepinephrine). You decide to perform an adrenocorticotrophic hormone (ACTH) stimulation test, the results of which show that the patient is a 'high nonresponder' (i.e. the baseline level is high and there is no increase after ACTH stimulation). You wonder about the benefit of administering steroids to reverse shock in this setting.

Pro: A blunted response to ACTH strongly suggests adrenal failure

Djillali Annane

Disruption of the hypothalamic–pituitary–adrenal (HPA) axis, a major actor in the host response to stress, occurs in about half of patients with vasopressor-dependent septic shock and is responsible for high rates of mortality [1,2]. A number of clinical trials reported during the past 15 years have demonstrated that a prolonged course (5–11 days) of low to moderate doses of hydrocortisone (200–300 mg/day) alters positively the clinical course of septic shock. Indeed, a meta-analysis of these trials [3] revealed a significant increase in the proportion of patients in whom shock was reversed by 7 days with corticosteroid use (relative risk [RR] = 1.60, 95% confidence interval [CI] = 1.27–2.03). Furthermore, mortality rates at 28 days in patients with septic shock were dramatically reduced with corticosteroid use (RR = 0.77, 95% CI = 0.65–0.90). The authors of the meta-analysis suggested that corticosteroids should be given only to patients with demonstrable blunting of the HPA axis (i.e. those with a cortisol increase of ≤9 μg/dl after receipt of 250 μg ACTH [so-called 'nonresponders']), whereas another meta-analysis of these trials [4] claimed that the benefit from corticosteroids was unrelated to the cortisol response to exogenous ACTH stimulation.

The discrepant conclusions from these systematic reviews relates mainly to the fact that separate data for adrenal insufficiency were available in only two of the studies [5,6]. However, different definitions of adrenal insufficiency were used. In the first trial [5] too few patients had adrenal insufficiency to permit any conclusions to be drawn. In the second trial [6] benefit from corticosteroids was demonstrated only in those patients who exhibited a cortisol increase ≤9 μg/dl after receiving 250 μg ACTH. This latter trial contributed about 70% to the findings of the meta-analyses [3,4]. A recent single-centre, placebo-controlled, randomized trial [7] also demonstrated that, compared with placebo, the likelihood that hydrocortisone would induce shock reversal was greater in 'nonresponders' than in 'responders'. Thus, the current evidence-based conclusion is that nonresponders to ACTH draw greater benefit from corticosteroids than do responders.

ACTH = adrenocorticotrophic hormone; CI = confidence interval; HPA = hypothalamic–pituitary–adrenal; RR = relative risk.

Some people argue that sepsis is characterized by high baseline cortisol levels, rendering the ACTH test invalid in this context. They believe that the adrenals are exhausted. However, it was clearly established in animals that sepsis was associated with high circulating levels of corticosterone and with low adrenal tissue concentration of the hormone [8]. Almost a century ago, it was shown in patients with severe sepsis that high circulating cortisol levels depended more on impaired cortisol clearance from plasma than on increased synthesis [9]. This finding was subsequently corroborated by a lack of correlation between baseline and absolute increment in cortisol levels after ACTH administration [1,2]. Let us consider the view that the adrenals are exhausted in septic shock. A very small amount of cortisol is stored in the adrenal glands, and the rate of secretion is closely dependent on the rate of biosynthesis [10]. Following ACTH administration, cholesterol is rapidly mobilized to the mitochondrial side-chain cleavage enzyme to produce cortisol through several enzymatic steps [11]. Exhaustion of the adrenals would mean that cortical cells are downregulated during sustained stress. However, it has been shown that adrenocortical cells are upregulated in response to excessive stimulation [12]. Thus, one may actually expect a greater cortisol increment after ACTH stimulation in patients with high circulating levels.

In this young woman with severe and sustained stress, as indicated by very high circulating cortisol levels, the nonresponse to ACTH strongly suggests impaired adrenal function. Therefore, the patient will benefit from a replacement dose of corticosteroids.

Con: Clinical equipoise remains for steroid use in non-responders

Eddy Fan and Margaret S Herridge

Five clinical trials have examined the role of low-dose corticosteroids in septic patients [5,6,13-15]. The largest of these trials randomly assigned 300 patients either to low-dose hydrocortisone (300 mg/day) and fludrocortisone (50 μg/day) or to placebo [6]. Nonresponders to the 250 μg ACTH stimulation test (defined as those patients in whom cortisol level did not rise >9 μg/dl from baseline) and who received steroids had improved survival and shorter duration of vasopressor dependence compared with nonresponders who did not receive steroids. A meta-analysis of these low-dose steroid trials [16] showed a consistent and beneficial effect of low-dose steroid administration on survival and shock reversal.

Nonresponders with a high baseline cortisol, such as patient described in the present scenario, have an extremely poor prognosis [2], but should this patient receive steroids? Indeed, use of low-dose steroids was endorsed in the recommendations for the management of septic shock by the Surviving Sepsis Campaign [17]. However, several issues arising from the study conducted by Annane and coworkers [6], which represents nearly 75% of patients included in the meta-analysis [16], makes this question difficult to answer definitively. Several important observations deserve emphasis, and these include the lack of improvement in crude 28-day mortality rates when comparing all patients who received steroid with all of those who received placebo, a trend toward harm in responders who received steroids, and the inclusion of patients who received pharmacologic adrenalectomy with etomidate before enrolment. These observations raise important questions about the true efficacy and safety of exogenous steroids in patients with septic shock and in those without iatrogenically induced (e.g. etomidate) relative adrenal insufficiency.

Furthermore, recent work suggests that glucocorticoid secretion increases under the stress of critical illness, with a concomitant decrease in circulating levels of corticosteroid-binding globulin [18]. Thus, measures of total serum cortisol (as assessed in the study conducted by Annane and coworkers [6]) may not accurately reflect levels of biologically active free cortisol, which may be normal or elevated in the hypoproteinaemic patient [19]. The diagnosis of relative adrenal insufficiency in the critically ill is further complicated by the lack of a standard definition of appropriate adrenal response in these patients and controversy over the use of low-dose or high-dose ACTH stimulation tests [20-23]. Patients with moderate to high baseline cortisol levels (e.g. >25 μg/dl) who do not respond to ACTH stimulation may lack 'adrenal reserve' but they may not have relative adrenal insufficiency, and therefore they may not benefit from steroid treatment (the patient referred to in the scenario presented above falls into this category) [21,24]. Finally, increasing awareness of the detrimental effects of steroids on the development of critical illness neuromyopathy must lead clinicians to re-evaluate the risks and benefits of exogenous steroid use in these patients [25]. Unfortunately, follow up of patients in the study conducted by Annane and coworkers [6] did not track this important outcome.

Taken together, these uncertainties lead to ongoing clinical equipoise regarding the use of steroids in patients with septic shock [26]. Until rigorous definitions and diagnostic tools for identifying relative adrenal insufficiency in the critically ill are established, and further randomized clinical trials confirm their therapeutic benefit, one should consider very carefully whether routine administration of steroids for septic shock is appropriate. The results of the ongoing European CORTICUS study (Corticosteroid Therapy of Sepsis and Septic Shock) will hopefully provide some answers to these important questions.

Pro's response: Role of etomidate

Djillali Annane

The issue of etomidate is crucial. First, it is now obvious that, in septic shock, a single bolus of etomidate is associated with sustained blunting of the HPA axis and increased mortality – an effect that is fully reversed by a replacement dose of corticosteroids [27]. Clearly, in the French phase III trial [6], treatment with low-dose corticosteroid was also associated with reduced mortality in etomidate-free septic shock (odds ratio = 0.40, 95% CI = 0.19–0.82). Because exogenous ACTH injection has no effect on albumin or corticosteroid-binding globulin levels, the increment in total cortisol following ACTH directly reflects the increment in cortisol synthesis, and thus one can use delta cortisol (cosyntropin stimulated minus basal total cortisol) as a reliable index of cortisol synthesis in the critically ill. The patient described in the scenario above had a basal cortisol greater than 34 μg/dl and a delta below 9 μg/dl, and was thus very likely to die from septic shock [2]. *Post hoc* analysis of data from the French multicentre trial [6] showed that such nonresponders with high basal cortisol levels also benefited from corticosteroids. Indeed, 12 deaths (out of 16) occurred among placebo-treated patients and three (out of nine) occurred in the corticosteroid-treated patients (RR = 0.44, 95% CI 0.17–1.17). As far as muscle weakness was concerned, there was only one out of 150 corticosteroid-treated patients in whom neuromuscular disorders were reported at the time of hospital discharge (unpublished data). In addition, corticosteroid treatment was associated with improved long-term (1 year) survival. Thus, in practice, septic shock patients who are nonresponders to the ACTH test (such as the patient described in the scenario presented above) should receive 7 days of treatment with intravenous bolus of 50 mg hydrocortisone every 6 hours plus 50 μ g oral fludrocortisone once daily, regardless of baseline cortisol levels.

Con's response: Definition of relative adrenal insufficiency is still unclear

Eddy Fan and Margaret S Herridge

Recent work has suggested that critically ill patients with functionally intact HPA axes should achieve stress-induced cortisol levels in excess of 25 μg/dl [21,24]. These patients, like the patient presented in the scenario above, are already maximally stimulated and are unlikely to respond to an ACTH stimulation test. In fact, lack of an 'appropriate' rise in cortisol levels following ACTH administration has been demonstrated in healthy volunteers and in critically ill patients without evidence of HPA dysfunction [28,29]. To date, there are no natural history data in sepsis patients to help us understand how the magnitude of cortisol levels varies during the episode of critical illness and in response to a variety of stressors. Thus, there is significant uncertainty about how we should define and therefore diagnose relative adrenal insufficiency in critically ill patients. In light of this, a trend toward unfavourable outcomes among nonresponders with septic shock [6] and the aforementioned potential adverse effects, we do not believe that routine steroid administration is warranted in these patients, given the current state of clinical evidence.

Competing interests

The authors declare that they have no competing interests.

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