Relative adrenocorticoid insufficiency exists and should be treated

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ABSTRACT

The issue of relative adrenocortical insufficiency (RAI) in septic shock is confused and uncertain. Multiple definitions of RAI have been proposed, but it is most commonly defined as an increment of less than 250 nmol/L in total serum cortisol level after administration of 250 μg corticotropin. RAI is associated with an increased risk of death, after adjustment for other factors that might independently influence risk. It is likely that the definition of RAI, if it exists, will be modified in the future, based on research that measures the level of free serum cortisol (the active fraction), rather than total serum cortisol (as currently measured). There is strong, but not overwhelming, evidence that administration of low doses of hydrocortisone to patients with septic shock, especially those with RAI, improves survival.

Crit Care Resusc 2006; 8: 371–375

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The issue of relative adrenocortical insufficiency (RAI) in septic shock is confused and uncertain. This is a consequence of the use of different definitions and measurement methods, uncertain or incomplete interpretation of results, and questions about internal and external validity of trials. It can be said with certainty only that:

- something not yet fully understood happens to adrenocortical function during septic shock;
- this abnormality is strongly associated with decreased likelihood of survival (although not necessarily causal); and
- treatment of septic shock with low doses of hydrocortisone, at least in some patients, appears a highly promising, but still unproven, adjunctive therapy.

In this article, I will consider first the abnormalities of adrenal physiology during septic shock and then the role of treatment with low-dose hydrocortisone.

Assessment of adrenocortical function in septic shock

The assessment of adrenocortical function is complicated by issues which include:

- whether to measure free or total serum cortisol levels;
- the significance of baseline (unstimulated) versus stimulated levels of cortisol; and
- the significance of site of measurement (serum versus tissue) (Table 1).

The method most commonly used in both clinical practice and research studies is the 250 μg (high-dose) corticotropin stimulation test (CST). This measures total serum cortisol at baseline, and 30 and 60 minutes after administration of 250 μg tetracosactrin (synthetic corticotropin). In patients with septic shock, mean baseline serum cortisol levels are higher (850 nmol/L in 402 patients from five studies) than the maximum baseline level of 500 nmol/L observed in healthy control subjects.[5] Several studies have reported relationships — both positive and negative — between baseline serum total cortisol and survival. The most definitive of these studies (based on sample size and attempts to adjust for potential confounding by severity of illness) was conducted by Annane et al.[3] This showed that high baseline serum cortisol (> 940 nmol/L) and a lower increment after corticotropin stimulation (< 250 nmol) were both independently associated with mortality, after adjustment for multiple factors associated with severity of sepsis. While many different cut-off points and definitions have been proposed for RAI, increasingly the term is synonymous with a high-dose CST increment of total cortisol less than 250 nmol/L. The incidence of RAI ranges in different studies from about one third to two thirds of patients with septic shock.[2,3]

However, there are potential problems associated with the 250 μg CST. These include inaccuracy of the assays commonly used to measure total cortisol, uncertainty about the optimal stimulating dose of corticotropin,[4] and the possibility that tissue cortisol levels or end-organ resistance may be more relevant than serum cortisol levels.[6,7] Yet, the greatest uncertainty arises from the possibility that free serum cortisol level is a more valid measure of adrenocortical function than total serum cortisol level.

The site of action of cortisol is intracellular. Within the circulation, cortisol exists as a free bioavailable fraction (about 10%) and a fraction bound to plasma proteins, predominantly cortisol-binding globulin and albumin (about 90%).[6] In non-critically ill patients, it is a valid assumption that total (free and protein-bound) cortisol in the serum (not the site of action) correlates closely with intracellular total (free) cortisol.[6] However, there is strong evidence that

Table 1. Options for assessing adrenocortical function

Type of test and technique	Comments
Total versus free serum cortisol	
Total cortisol (mostly protein-bound and not active)	➢ Does not measure active fraction ➢ Substantial test variability
Free cortisol (biologically active)	
• Equilibrium dialysis	➢ Technically demanding but "gold-standard" ➢ Research technique only[1]
• Free cortisol index	➢ Indirect estimation of proportion of total cortisol that is free, acquired from measurement of total cortisol and cortisol-binding globulin ➢ Not widely available; research technique only ➢ Still relies on measurement of total cortisol[2]
• Ultrafiltration/ ligand binding	➢ Research technique only ➢ Validated against equilibrium dialysis[2]
Baseline versus stimulated	
Baseline (total cortisol)	➢ High baseline associated with increased risk of death[3]
Stimulated (total cortisol)	
• 250 μg tetracosactrin (synthetic corticotropin)	➢ Small increment associated with increased risk of death[3]
• 1 μg tetracosactrin (synthetic corticotropin)	➢ Not validated, but may have advantages over 250 μg test[4]
Sampling site	
Serum	➢ Easily accessible, uncertain relationship to levels at site of action
Tissue or intracellular	➢ No validated test

this relationship is not maintained in critically ill patients, largely because of decreased concentrations of binding proteins in the circulation.[1,2]

Hamrahian et al used equilibrium dialysis to measure serum levels of free cortisol in critically ill patients (only some of whom had sepsis).[1] Baseline and corticotropin-stimulated levels of total cortisol were lower in patients with low serum albumin levels, but free cortisol levels were similar in critically ill patients irrespective of serum albumin level, and were substantially higher than levels in normal patients. Most patients with abnormal high-dose CST results had low levels of serum albumin, and the baseline and stimulated levels of free cortisol were high-normal or elevated. The study concluded that the conventional CST could produce false positive results, as a consequence of low albumin levels.[1]

Similar results were reported by Ho et al in a study of patients with sepsis and septic shock.[2] They measured free serum cortisol using an ultrafiltration and ligand-binding assay, which was validated against the "gold standard" of equilibrium dialysis. They also calculated the free cortisol index by measuring total cortisol and adjusting for the concentration of cortisol-binding globulin. Free cortisol levels were elevated 10- to 15-fold, and correlated with the severity of sepsis. The increments in stimulated free cortisol levels were higher in patients with septic shock (192 nmol/L) than in patients with sepsis (115 nmol/L), which were higher again than in healthy control subjects (59 nmol/L). Among patients with septic shock, those who had conventionally defined RAI had higher free cortisol levels than corticotropin-responders (287 nmol/L versus 140 nmol/L), but also had lower increments in free cortisol (59 nmol/L versus 252 nmol/L). Both these studies provide strong support for the concept that free serum cortisol levels are a better reflection of cortisol status than total serum cortisol levels.

The study by Ho et al, which specifically studied patients with septic shock, provides evidence that attenuation of the response to corticotropin probably does occur, and in the same patients whether measured using free or total cortisol. A useful next step would be to study the association between cortisol levels (free and total, at baseline and after corticotropin administration) and survival after adjustment for severity of illness. This is necessary to determine the validity of the concept of RAI and to define it optimally.

Adrenocortical abnormalities in septic shock

Irrespective of the method of measurement, it seems likely that there is an association between some aspects of abnormal adrenocortical function and survival from septic shock. This association persists, at least for measurements using total cortisol, after adjustment for severity of illness. Although this provides strong support for the hypothesis that abnormalities in adrenal function contribute directly to the death of patients with septic shock, I do not believe it is sufficient to prove this hypothesis. There are at least two alternative explanations: that the association is not valid because of unadjusted confounding by severity of illness; or that the association is real, but abnormalities of adrenal function are not on the direct causal pathway between sepsis and death.

There are five possible, and not necessarily mutually exclusive, explanations for observed abnormalities of adrenal function in septic shock:

- absolute adrenal insufficiency;
- cortisol levels are appropriate and part of a normal physiological response;
- "relative adrenal failure" (the adrenals should be producing more cortisol);
- adrenal cortisol production is maximally stimulated (and cannot respond further to corticotropin stimulation); or
- levels of cortisol are elevated because of low tissue levels of cortisol or end-organ resistance to its effects.

I will consider each of these possibilities.

Absolute adrenal insufficiency: There is little evidence to suggest that absolute adrenocortical insufficiency is common in patients with septic shock. The occurrence of high baseline levels of cortisol (especially free cortisol), irrespective of increment in serum cortisol following a CST, makes absolute adrenal insufficiency unlikely. The only exception might be after administration of drugs that inhibit the synthesis of cortisol (eg, etomidate).[8,9]

Cortisol levels are appropriate and part of a normal response: The results reported by Hamrahian et al suggest that there is no functional abnormality of adrenocortical function:[1] free cortisol levels are appropriately raised because of the stress response or end-organ resistance; and false-positive results arise on the CST when total cortisol is measured because of low albumin levels. Most patients in this study did not have sepsis, and among those with sepsis it is unclear how many had septic shock. Results reported by Ho et al[2] do not tend to support this hypothesis.

Relative adrenal failure: A possible concept of RAI is that cortisol levels are normal or elevated, but should be even higher. This is reflected by the failure of corticotropin to stimulate additional increments of cortisol and might arise from sepsis-induced cellular dysfunction of the adrenal gland. This hypothesis is consistent with the observed results, but cannot be distinguished from alternative explanations outlined below.

Cortisol is maximally stimulated: Another possible concept of RAI is that there is nothing *per se* wrong with the adrenals, but that they are maximally stimulated and can produce no more cortisol. This might simultaneously explain high baseline levels of cortisol (especially free cortisol) and poor incremental response to corticotropin. It is possible that these patients might benefit from higher levels of cortisol because of a pharmacological, rather than physiological, effect of corticosteroids.

Low tissue cortisol or end-organ resistance: The final possible concept of RAI is once again that there is nothing *per se* wrong with the adrenals, and that elevated free cortisol levels arise as a consequence of either low tissue levels or resistance to the action of cortisol in end organs.[7] Additional supplemental steroids might be of benefit if resistance is substantial and able to be overcome by higher cortisol levels.

Defining RAI will require larger studies that measure free cortisol and explore relationships between abnormalities of adrenal function and survival. Such studies should focus especially on the issue of whether corticotropin stimulation identifies a group that has true attenuation of responsiveness, or whether such changes might be confounded by levels of binding protein. An additional barrier in performing such studies is that, if patients are treated with steroids, and the relationships between abnormal adrenal function and survival are real, such an effect might be lost after treatment.

Role of low-dose hydrocortisone in septic shock

I will focus here on the role of low-dose hydrocortisone in the management of septic shock. I will not discuss its established effect, to reduce vasopressor dosage and duration, or the role of fludrocortisone.

Enthusiasm for the use of glucocorticoids in the treatment of septic shock has waxed and waned over several decades. There has been a renaissance in their popularity, associated with the hypothesis that low doses of hydrocortisone improve survival, at least in selected patients with RAI. Whether this is proven, and the treatment becomes established, or whether it wanes with new data remains to be determined.

There are three broad possibilities with respect to the efficacy of low doses of hydrocortisone in septic shock:

- it is not effective (or harmful) in all (unselected) patients, and no subgroup which benefits can be identified;
- it is effective in all (unselected) patients, and no subgroup that fails to benefit can be identified;
- it is effective in some (selected) patients and not effective (or harmful) in other groups of patients.

The available data most strongly (but not overwhelmingly) support the second or third options, and there is uncertainty as to whether the subgroups that benefit have been optimally defined.

Evidence from Annane et al[10]

The largest and most widely quoted study of low-dose steroids was that conducted by Annane et al.[10] This was a large, well conducted, double-blind placebo-controlled trial that used valid inclusion and exclusion criteria to identify a population with septic shock. The population was randomised to a 7-day course of either intravenous hydrocorti-

sone (50 mg, 6-hourly) and oral fludrocortisone (50 μg daily), or indistinguishable placebo. The main issues relating to the internal validity of this trial are that the analysis was not conducted using the "intention-to-treat" principle, and that the primary end-point was survival time during the first 28 days (rather than the proportion of patients who survived, assessed at 28 days). The major issue relating to external validity is the possibility that the use of the drug etomidate, which is not used in many parts of the world because of its capacity to induce absolute adrenocortical insufficiency, influenced responsiveness to steroids.

There has been disagreement about the appropriate end-point for clinical trials that aim to establish the efficacy of therapeutic interventions in sepsis. I believe that the only appropriate end-point is the proportion of patients alive (ie, survival as a dichotomous yes/no variable) at a clinically meaningful time point after randomisation. The minimum clinically meaningful time point is 28 days, but 90 days, hospital discharge, or even 1 year may be better. No-one would advocate the proportion of patients who suffer a "slow lingering death" as an end-point for sepsis trials, but this could be the unintended consequence of using survival time as an end-point. An intervention that delays but does not prevent death will result in increased survival time, without increasing the proportion of patients who actually survive. Its only real effect is to increase the proportion of patients who have a slow lingering death.

The primary end-point for Annane et al's trial was survival time, and not the proportion of patients alive at 28 days. The study reports an improvement in survival time for patients randomised to steroids, who were non-responders to corticotropin (hazard ratio, 0.67; 95% CI, 0.47–0.95).[10] Among non-responders, the median time to death was 24 days for steroid-treated patients, compared with 12 days for those receiving placebo. However, in an analysis not reported in the study, the proportion of patients alive at 28 days among non-responders was 60/114 for patients randomised to placebo and 73/115 for patients randomised to low-dose steroids. This difference favours the intervention, but there is a reasonable probability it arose by chance (χ^2 test, $P = 0.13$). The trend is encouraging, but, when the data are analysed using a clinically significant end-point, the study is essentially underpowered to detect a clinically significant difference in survival.

The second common criticism of this study relates to its separate analysis of corticotropin-responders and non-responders. There is a strong biological rationale as to why response to steroids might differ between these groups. However, as conducted, the trial enrolled and randomised patients at a time when their response to corticotropin was not known. As such, the "purist" intention-to-treat analysis is a comparison of survival at 28 days in all patients randomised to placebo compared with those randomised to steroids. This analysis shows no difference between groups at 28 days (82/150 versus 91/149; $P = 0.45$). Any additional analysis of subgroups, even if specified before the trial began, is essentially post-hoc analysis, and should be regarded as hypothesis-generating rather than definitive. Some will accept this post-hoc analysis because it was specified *a priori* and because of the biological rationale, while others will interpret it as an encouraging result that should stimulate a new trial in which patients with septic shock are randomised to steroids or placebo, with randomisation stratified by responsiveness to corticotropin.

Etomidate is widely used in Europe as an induction agent in critically ill patients, because it has little blood pressure-lowering effect. However, etomidate is known to induce adrenocortical insufficiency,[9,11] and observational studies have reported a strong association between use of etomidate and death in critically ill patients with multiple trauma.[8] It has subsequently been reported that 24% of patients randomised in Annane et al's trial received etomidate in the 24 hours immediately preceding randomisation, and whether additional patients received the drug more than 24 hours before randomisation has not been clarified.[10] If etomidate induced adrenocortical insufficiency in some patients (who would presumably have been non-responders to corticotropin), it is at least possible that some of the beneficial effects reported in this study arose from the treatment of etomidate-induced absolute adrenal insufficiency. This would not have any influence on the internal validity of the trial, but might have substantial impact on its external validity (ie, similar results may not be obtained in populations not exposed to etomidate).

Evidence from meta-analyses

Two meta-analyses have combined five trials of low-dose steroids (including the trial by Annane et al[10]), with broadly similar results.[12,13] These meta-analyses pooled the intention-to-treat results for survival at 28 days or hospital discharge, rather than survival time. The results suggest a clear benefit of treatment with low-dose hydrocortisone for patients with septic shock, irrespective of corticotropin response (relative risk [RR] at hospital discharge, 0.83; 95% CI, 0.71–0.97). However, as the only large study that presented results for corticotropin-responders and non-responders was Annane et al's own trial,[10] the meta-analyses have not been of use in determining whether there are subgroups of patients who benefit more, or less, from low-dose hydrocortisone.

These meta-analyses have been criticised for not including two older trials that reported worse outcomes after treatment with low-dose hydrocortisone.[14,15] However, these trials had poor methodological quality, and enrolled

patients with infection or sepsis, only some of whom had septic shock. Since the meta-analyses were conducted, a further randomised controlled trial of continuous infusion of hydrocortisone has reported a survival benefit.[16] On balance, it is reasonable to conclude that there is strong evidence for the effectiveness of low-dose hydrocortisone in patients with septic shock. The only caveat is that all studies were performed in countries where etomidate is available.

The future

Corticus (Corticosteroid Therapy of Septic Shock) is a large (800 patient), European-based trial of low-dose hydrocortisone compared with placebo that has now completed recruitment (http://www.clinicaltrials.gov/ct/show/NCT00147004). The primary end-point is 28-day mortality in all patients who do not respond to corticotropin, and the secondary end-points are 28-day all-cause mortality in the total group and in corticotropin-responders, intensive care unit and hospital mortality, 1-year mortality, reversal of organ system failure, especially shock, and duration of ICU and total hospital stay. This study should provide a definitive conclusion, especially if concomitant data about etomidate use have been collected.

Abnormalities of adrenocortical function have been described and appear likely to be associated with risk of death. Whether these abnormalities are caused by RAI and, if so, what RAI actually is, remains to be determined. It appears likely that low-dose hydrocortisone treatment improves survival in patients with septic shock. It remains to be determined whether this treatment is effective in unselected patients or only in those with derangements of adrenocortical function.

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