Relative adrenal insufficiency in sepsis: match point or deuce?

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The annual incidence of severe sepsis in the adult Australian population is 0.77 per 1000 population, corresponding to 15 700 new cases each year.[1] Despite advances in therapy, the mortality rate is about 37.5% in sepsis and 50%–60% in septic shock. The basis for corticosteroid supplementation in septic shock is thought to be the presence of a syndrome termed "relative adrenal insufficiency" (RAI). The Surviving Sepsis Campaign Guidelines of 2004 endorsed the use of steroids in the management of septic shock with the following recommendations:[2]

- intravenous hydrocortisone, 200–300 mg/day for 7 days (Grade C recommendation);
- 250 μg corticotropin stimulation test (CST) (Grade E recommendation);
- addition of 50 μg of fludrocortisone to hydrocortisone (Grade E recommendation); and
- avoidance of high-dose steroids (> 300 mg hydrocortisone/day) (Grade A recommendation).

However, both the use of steroids and the diagnosis of RAI in septic shock have been sources of intense controversy. Publication of the results of a recent study of steroids in acute respiratory distress syndrome (ARDS), which demonstrated either no benefit or even excess harm in the steroid group,[3] adds fuel to this debate. It is therefore timely to review the history of the evolution of steroid therapy in sepsis and to explore the diagnostic criteria for RAI.

Background

Hydrocortisone was introduced into clinical practice by Hench in 1950, and steroids were first used for the management of sepsis in patients with poststreptococcal infections in 1951.[4] Since then, therapy with this drug has undergone several transformations from "steroid success" in sepsis and malaria in the 1970s and early 1980s[5,6] to "steroid excess" (30 mg/kg methylprednisolone) in severe sepsis in the mid to late 1980s.[7] The high-dose steroid approach resulted in excess morbidity and mortality in the steroid group, leading to total abandonment of steroid use in the early 1990s. However, this phase was short-lived. The driving forces behind the renaissance in steroid use were data from randomised controlled trials comparing hydrocortisone to placebo, which showed improved haemodynamic status and vasopressor weaning with the use of steroids,[8] along with results from the European meningitis study, which demonstrated improved outcome with the use of steroids.[9]

In 2002, Annane et al published the results of a prospective randomised trial of steroids in septic shock, which showed decreased mortality in the steroid group.[10] More recently, a trial of steroids in hospitalised patients with community-acquired pneumonia also showed reduced mortality.[11]

The Annane study, the largest randomised controlled trial of steroids in septic shock, has been criticised on a number of counts: errors in trial design, change of protocol during the study, and the inclusion of patients who had received etomidate (a known adrenal suppressant). Consequently, the incidence of RAI has likely been overstated.

The uncertainty and controversy generated from the Annane study prompted the initiation of the Corticus study.[12] This European multicentre, randomised trial of steroids versus placebo in septic shock[7] was stopped prematurely because of a poor recruitment rate, problems with the cortisol assay (described later), and marked differences in population profile compared with the original study. The prime reason for the poor recruitment rate was that there was not sufficient clinical equipoise among the investigators not to use steroids — they felt there was a prima facie case for routine steroid use, once septic shock was diagnosed. Data presented at the European Society of Intensive Care meeting in Barcelona in September 2006 suggest that there were no significant differences between the steroid and the placebo groups in terms of mortality from septic shock.

A French multicentre study is currently underway comparing hydrocortisone to hydrocortisone plus fludrocortisone in septic shock. However, this does not address the main question — are steroids better than placebo in septic shock? Adding to the current uncertainty are concerns about the safety of steroids in septic shock, which have resurfaced with publication of data from the ARDS Clinical

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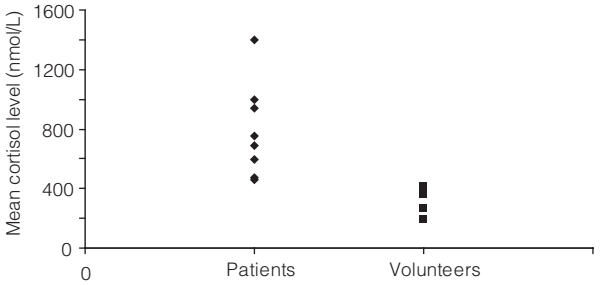
Figure 1. Mean plasma cortisol levels in critically ill patients (eight studies[15-22]) and control volunteers (four studies[23-26])



Trials Network, which found increased myopathy and reintubation rates after steroids,[3] and from Louillet et al, which found increased neuropathy and myopathy.[13]

In Australia and New Zealand, clinical opinion is divided on both the role of steroids and the tests to identify RAI. An electronic survey of 70 intensivists in the two countries by Venkatesh and Cooper in February 2006 revealed that 60% routinely use steroids in patients with septic shock (unpublished data). The trigger for initiation of steroids varied widely, from any requirement for vasopressor to requirement for 50 μg noradrenaline. Only 50% of intensivists who routinely use steroids perform a CST beforehand, and only 25% of the 40% who do not routinely use steroids perform a CST. There is clearly a lack of consensus among intensivists on the role of steroids in sepsis and the indications for their use.

Thus, despite extensive observational data and a large clinical trial, debate continues in Australia about the role of steroids in patients with septic shock. At the heart of this debate is the question of the incidence (and indeed the existence) of RAI in patients with septic shock.

What is relative adrenal insufficiency, and why the controversy?

Absolute adrenocortical insufficiency (diagnosed by very low total plasma cortisol concentrations) is uncommon in intensive care patients. However, the term RAI was coined to describe a syndrome where the adrenal glands partially respond to stress, but the magnitude of response is not commensurate with the degree of stress. A number of diagnostic criteria have been developed,[14] including an inappropriately decreased baseline total plasma cortisol level or a reduced cortisol response to corticotropin, as this has been associated with vasopressor requirement and higher mortality in severe sepsis. However, the optimal diagnostic criteria are controversial. The reasons include:

- uncertainty about the optimal diagnostic test for RAI; and
- lack of a consistent relationship between random serum cortisol levels or cortisol response to corticotropin and outcome.

We explore these issues in more detail in the following section.

Areas of uncertainty in diagnostic testing for RAI

Appropriate baseline cortisol?

As noted above, a criterion used to define RAI is inadequate increase in baseline cortisol during stress. However, it is unclear what constitutes an appropriate baseline cortisol level in the critically ill patient. Studies have demonstrated a wide range of elevated total plasma cortisol concentrations in stressed intensive care unit patients[15-22] compared with healthy volunteers[23-26] (Figure 1). Thus, it is difficult to define a reference range for critically ill patients. Investigators have proposed a range of baseline plasma cortisol values during severe stress to diagnose RAI — 415 nmol/L, 500 nmol/L and 550 nmol/L.

Venkatesh et al recently published a study involving hourly measurements of total plasma cortisol in 21 critically ill patients with sepsis, finding significant variability in plasma concentrations both between and within patients.[27] The individual mean plasma cortisol ranged from 286 (SD, 59) nmol/L to 786 (SD, 93) nmol/L. Large variability in plasma cortisol meant that reliable classification of patients as "presence of RAI" or "no RAI" was not possible with this parameter. A "gold standard" value for the diagnosis of RAI in ICU patients based solely on baseline plasma cortisol level does not exist.

Plasma free cortisol

Most circulating cortisol (90%) is bound to cortisol-binding globulin, and a small proportion to albumin. About 5%–8% is free, and only this free fraction possesses biological activity. During critical illness, levels of cortisol-binding globulin and albumin decrease,[28] and free cortisol levels increase.[29] Data from Ho et al have also demonstrated elevations in plasma free cortisol in septic shock.[30] They found that basal total and free cortisol concentrations were significantly higher in the septic shock group than in the sepsis and control groups. Free cortisol increments corresponded to the presence of sepsis and its severity, whereas total cortisol increments did not.[30] Supportive evidence for elevations in plasma free cortisol also comes from the work of Venkatesh et al, who demonstrated elevated mean urinary free cortisol (865 [SD, 937] nmol/L; reference range, 100–300 nmol/L),[27] and Cohen et al who demonstrated elevated salivary cortisol levels[31] (which are predominantly the free fraction) in critically ill patients. Plasma free cortisol

Table 1. Summary of data on prevalence of relative adrenal insufficiency (RAI)*

Study	Cortisol cutoff (nmol/L)	RAI prevalence (%)
Baseline total plasma cortisol		
Rydvall[45]	< 400	36%–47%
Hamrahian[29]	< 415	38%
Moran[34]	< 500	32%
Offner[46]	< 500	60%
Schein[21]	< 550	5%
Marik[47]	< 690	61%
Plasma cortisol response to corticotropin		
Sibbald[19]	< 125	19%
Bollaert[8]	< 165	29%
Rydvall[45]	< 200	56%
Moran[34]	< 200	67%
Rothwell[32]	< 250	41%
Bouachour[15]	< 250	75%
Annane[18]	< 250	77%

* Adapted from de Jonghe et al, International Symposium on Intensive Care and Emergency Medicine (ISICEM) Year Book 2006: 539-51. ◆

provides a better assessment of adrenal function than total cortisol because:

- It is the biologically active hormone;
- Cortisol-binding globulin and albumin levels decrease in critical illness leading to increases in plasma free cortisol;
- The relationship between total and plasma free cortisol is non-linear, and thus plasma free cortisol concentrations cannot be predicted from total cortisol values; and
- Plasma free cortisol increments corresponded to sickness severity, whereas total cortisol increments did not.[30]

However, minimal data exist on changes in plasma free cortisol after corticotropin stimulation or on the relationship between plasma free cortisol and outcome. It is clear that free cortisol dynamics need further clarification in critical illness.

Tests of dynamic adrenal reserve: the corticotropin stimulation test

The CST measures the 60-minute total plasma cortisol response to parenteral administration of 250 μg of synthetic corticotropin. Both the dose of corticotropin and the cortisol response that predicts outcome are subject to debate.

The normal CST response in unstressed volunteers is a rise in serum cortisol levels to above 500–550 nmol/L, or an increase of more than 250 nmol/L from baseline. While an increment < 250 nmol/L is the threshold for diagnosing RAI, pooled data from other studies suggest that the threshold increment which may better predict outcome is closer to 400 nmol/L.[15,18,19,32-39] The limitation of using total (rather than free) cortisol response was demonstrated by Hamrahian et al in critically ill patients.[29] Although patients were classified as CST non-responders and responders based on total cortisol response (205 nmol/L versus 318 nmol/L), the changes in plasma free cortisol were similar in the two groups (113 nmol/L versus 132 nmol/L).

The usual 250 μg dose results in supraphysiological plasma concentrations of corticotropin (65 000 pg/mL; reference range, < 100 pg/mL) and may override adrenal resistance to corticotropin and produce false-negative results in patients with mild secondary adrenal insufficiency. Consequently, a "low dose" CST (1 μg) has been suggested, which would result in more physiological concentrations, similar to those seen in the insulin hypoglycaemia test.[40]

The cortisol response elicited with the insulin test is also comparable to that seen with the low-dose test.[41] Data from Abdu et al clearly suggest that the low-dose test is superior for the identification of secondary adrenal insufficiency in non-critically ill patients.[42] More recently, a study from Europe suggested that the cortisol response to a low-dose CST may be better than the response to the 250 μg dose CST for predicting mortality and diagnosing RAI in critical illness.[43]

In summary, there is no consensus on the criteria for RAI, based on either total plasma cortisol or the corticotropin response (Table 1). The divergent criteria and the wide ranging prevalence of RAI seen in past studies are a testament to the lack of consensus and need for definitive evidence. A contributory factor to the high prevalence of RAI from European data may be the widespread use of etomidate.[44]

Variations in cortisol assay

The coefficient of variation of cortisol estimations is usually 10%–12%, and the same specimen submitted to different assays can yield significantly different results. We examined four different assays (HPLC, TDx, Immulite and Centaur), finding marked differences in plasma cortisol values for the same sample, depending on the assays used. Variable plasma cortisol results arising from the use of different assays or laboratories will greatly influence the interpretation of plasma cortisol and the corticotropin test. This was a serious limitation in the recently terminated Corticus study.

Plasma aldosterone

Low plasma aldosterone concentrations (expressed as aldosterone/renin ratio) — considered by some to be an indicator of adrenal insufficiency — have also been reported in sepsis.[48] Low plasma aldosterone concentrations and an inadequate response to corticotropin in septic shock have

been associated with renal failure and excess length of stay. The value of aldosterone as a marker for adrenal dysfunction needs validation in larger trials.

Other possible tests

Plasma corticotropin and corticotropin-releasing hormone stimulation tests investigate the integrity of the hypothalamic–pituitary–adrenal axis. However, few data are available on the usefulness of these tests in critically ill patients. Data from Venkatesh et al[27] suggest that plasma corticotropin level has no relationship with sickness severity, total plasma cortisol level and urinary free cortisol level, and thus may not be a useful index of adrenal function. The metyrapone and insulin hypoglycaemia tests have significant adverse effects and thus have no place in adrenal assessment in the ICU patient.

Lack of longitudinal assessment

Most studies have examined adrenal function at a single time point during patient hospitalisation. Sepsis and critical illness are dynamic processes with both up-regulation and down-regulation of inflammation over the course of hospitalisation. A longitudinal profile of adrenal function is needed to judge the extent of alterations.

In summary, there are significant limitations with the current methods used for diagnosing RAI in critically ill patients. This in turn affects the ability to define the relationship between plasma cortisol and outcome, as seen below.

Relationship between total serum cortisol or corticotropin response and outcome

Given the limitations of total cortisol as a measure of adrenal function in critically ill patients, it is not surprising that a reproducible relationship between total cortisol or the cortisol response to CST and outcome has been difficult to define.

A number of studies of mixed populations of ICU patients have suggested that higher cortisol levels are associated with a poor outcome.[18,34,49-51] Other studies have not confirmed these findings. In a study of 37 patients with sepsis, the median cortisol value was 1399 nmol/L (range, 430–1140 nmol/L), with no significant difference between survivors and non-survivors.[21] Similarly, in a study of 32 patients with sepsis, Rothwell et al documented a mean basal cortisol level of 728 nmol/L, which had no impact on mortality.[32] The findings of Bouachour et al[15] and Drucker[52] also do not suggest a relationship between plasma cortisol level and outcome. On balance, a clear relationship between total serum cortisol and outcome in critical illness (defined by mortality, organ dysfunction or vasopressor requirement) has not been demonstrable to date.

Similar considerations apply to the cortisol response to CST. As noted, while an increment < 250 nmol/L is the threshold for diagnosing RAI, and therefore an adverse outcome,[15,18,32,34,36] pooled data from other studies suggest that the threshold increment which may better predict outcome is closer to 400 nmol/L.[19,33,35,38]

Conclusions

It is evident that current methods for diagnosing RAI in patients with septic shock have significant limitations and are fraught with imprecision. We suggest that measurement of plasma free cortisol, utilisation of the 1 μg dose of corticotropin and longitudinal data on adrenal function may better represent adrenal function than total cortisol level measured on a single occasion. In Australia, a multicentre phase II observational trial to improve definition and identification of RAI has been designed and submitted in the current funding round of the National Health and Medical Research Council. To assist rational therapy with steroids for etomidate-free patients with septic shock, it is fundamental that optimal diagnostic criteria for RAI are developed. While we await the results of current trials, we note there is clear clinical equipoise (and marked differences of opinion among experienced ICU clinicians) for the use of steroids in patients with septic shock.

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