Adrenocortical function in critical illness

Most critically ill patients exhibit increased plasma cortisol concentrations. However, the report of Duggan, Browne and Flynn published in this issue of the journal serves as a reminder that adrenocortical insufficiency exists as a potentially treatable component of critical illness.

What constitutes normal adrenocortical function during critical illness remains unclear. Although there have been several reports on the subject, the conclusions are controversial. What is incontrovertible is that adrenocortical function is essential for host survival during critical illness. Doses of endotoxin or live Escherichia coli, which are sub-lethal in normal animals, are lethal when administered to adrenalectomized animals. In adrenalectomized primates receiving sub-physiological doses of corticosteroids, cholecystectomy produced marked cardiovascular instability compared with intact or adrenalectomized animals receiving supra-physiological doses of corticosteroids. Hypotension in the former resulted from decreased cardiac index and peripheral vascular resistance. This is not surprising as corticosteroids are known to enhance myocardial contractility and vascular smooth muscle tone in response to adrenergic stimuli, mainly by increasing adrenoreceptor sensitivity to catecholamines.

Investigators have measured plasma cortisol concentrations in different subgroups of critically ill patients. Those with bacterial infections, septic shock, and other acute medical or surgical conditions generally have increased plasma cortisol concentrations. Although the majority of studies report increased cortisol concentrations in critical illness, the range of measured concentrations is wide. They vary from those observed in healthy individuals to up to 20 times these values. This scatter makes it difficult to define a normal range for plasma cortisol concentrations in critical illness.

Some studies have reported a significant correlation between plasma cortisol and adrenocorticotrophic hormone (ACTH) concentrations in critical illness. This increase in pituitary secretion of ACTH may be at least partly responsible for increasing cortisol release from the adrenal gland. However, other studies have failed to demonstrate such a correlation, particularly in non-survivors, which suggests that in some patients the hypothalamic-pituitary-adrenal axis may be impaired during critical illness. Hypercortisolism in critical illness may result not only from increased adrenocortical release but also from a decreased rate of cortisol extraction from blood, lower cortisol binding globulin concentrations and reduced hepatic extraction.

The precise incidence of adrenocortical insufficiency in critical illness is unknown. Values ranging from 0% to 41% have been reported. Sibbald and colleagues assessed adrenocortical responsiveness in patients with septic shock using an ACTH stimulation test and reported a subnormal cortisol response in 19%. In a large series, Finlay and McKee found that 27% of critically ill patients had low plasma cortisol concentrations. In another study, they reported that 12 critically ill patients with low basal cortisol concentrations also had abnormal responses to ACTH. In a more recent study, 24% of patients with septic shock exhibited adrenocortical insufficiency after ACTH stimulation.

In contrast, only 3% of very sick patients were reported to have low random plasma cortisol concentrations. Moreover, another group found that only 2% of critically ill patients had abnormal responses to ACTH administration, and of these 50% had been receiving long-term corticosteroid medication. A variety of reasons may explain the wide range of reported incidences of adrenocortical insufficiency. These include: method used to diagnose adrenocortical insufficiency (basal plasma cortisol concentrations, response to ACTH stimulation, or both); use of cortisol normal ranges derived from healthy individuals to detect adrenocortical insufficiency in the critically ill; and absence of standardization in the design of these studies, particularly in defining patient groups.

The question of how adrenocortical function in critical illness should be assessed remains unanswered. Absolute adrenocortical insufficiency, which results in very low plasma cortisol concentrations, which alone may be diagnostic, is unusual in the critically ill. It may result from massive bilateral adrenal haemorrhage as a complication of coagulopathy or severe thrombocytopenia, adrenocortical suppression from long-term corticosteroid administration or drugs such as etomidate or ketoconazole. The diagnosis of relative adrenocortical insufficiency (supra-normal basal but deficient post-stimulation increase in plasma cortisol concentrations) is more controversial. Most investigators now regard an ACTH stress test as essential in the assessment of adrenocortical function. To date, most authors have introduced their own criteria for the diagnosis of adrenocortical insufficiency in critical illness. These are broadly similar to the values of basal and post-stimulation plasma cortisol concentrations used for the diagnosis of adrenocortical insufficiency in healthy individuals. Hypocortisolism appears to be common in septic shock. It has also been suggested that low plasma cortisol concentrations do not necessarily indicate functional adrenocortical insufficiency and that adrenocortical insufficiency can only be detected with certainty after an ACTH stress test. However, even if the values for increment and minimum peak plasma cortisol concentrations after ACTH stimulation observed in healthy individuals prove to be acceptable in making the diagnosis of adrenocortical insufficiency in the critically ill, there are still potential difficulties in interpreting the results. The absence of a post-stimulation peak in cortisol response in critically ill patients with high basal plasma cortisol concentrations would be difficult to explain. Whether this represents a state of maximally stimulated, and therefore appropriately functioning adrenal cortex or relative adrenocortical insufficiency, is still a matter for debate.
Certain factors in the patient’s medical history should lower the clinician’s threshold for diagnosing adrenocortical insufficiency in critical illness. These include the presence of a bleeding disorder, chronic steroid administration and the use of other adrenocortical suppressing drugs. Other important factors include a history of tuberculosis, metastatic malignancy and autoimmune disease. Moreover, there are subtle and less appreciated causes for adrenocortical dysfunction in critical illness. Hypopituitarism, either in its chronic form unmasked by critical illness, or its acute variant resulting from pituitary infarction or trauma, may be an important contributory factor to adrenocortical insufficiency in some patients. It may be suggested by other indirect indicators of hypothalamic–pituitary dysfunction, such as abnormal thyroid function tests. Hypotension may produce adrenal ischaemia and could be a cause of adrenocortical insufficiency. Bilateral adrenocortical haemorrhagic necrosis has been reported in 30% of patients who die from septic shock.24

Previous observations suggest that circulating mediators in critically ill patients can reduce the ability of adrenocortical cells to respond to ACTH. In vitro, adrenocortical cells produce less cortisol in response to ACTH after incubation with plasma from rabbits with septic shock compared with cells incubated with control plasma.25 The active component in that study may have been tumour necrosis factor-α (TNF-α) which has been shown to reduce the production of cortisol by human fetal adrenal cells.26 However, under certain conditions this cytokine can paradoxically stimulate adrenocortical function.27 A direct correlation between plasma TNF-α and cortisol concentrations was observed in patients with septic shock, but this relationship was not seen in septic shock complicated by adrenocortical insufficiency.18

Human lymphocyte-produced fragments of ACTH28 and corticostatin,29 an immune cell-derived peptide, can bind to ACTH receptors and thus decrease the response to endogenous ACTH. It is conceivable that high expressers of these molecules may be at risk of developing adrenocortical insufficiency during critical illness. It has been recognized recently that interleukin-6 (IL-6) can activate the pituitary–adrenal axis.30 Both IL-6 and ACTH concentrations were lower in critically ill patients with adrenocortical insufficiency compared with those with adequately functioning adrenal glands.31 These studies suggest that a deficient IL-6 response may contribute to adrenocortical insufficiency through understimulation of the pituitary–adrenal axis.

Some studies have suggested a relationship between plasma cortisol concentration and severity of illness.32 However, there has been no convincing evidence that measured increases in cortisol concentrations in critical illness are useful in predicting patient outcome.1 Many studies support the hypothesis that adrenocortical insufficiency in critical illness increases mortality.7 Adrenocortical insufficiency almost doubled mortality at 4 weeks from 44% to 80% in patients with septic shock.18 Furthermore, a subnormal response to ACTH in septic shock was associated with a significantly higher mortality.33 Although hypocortisolaemia was not uncommon in patients with septic shock and did not itself predict increased mortality, adrenocortical hyporesponsiveness was predictive of poor outcome.23 However, other studies have cast doubt on the belief that adrenocortical insufficiency is associated with increased mortality in critical illness. Schein and colleagues failed to find a relationship between low plasma cortisol concentrations and increased mortality.3 Others also reported that neither baseline nor peak plasma cortisol concentrations after ACTH stimulation were useful in predicting mortality in critically ill patients.1 In fact, higher plasma cortisol concentrations were found in non-survivors which suggests that high cortisol concentrations may be a marker of disease severity. This controversy has probably arisen because of the current imprecise definition and identification of adrenocortical insufficiency in critical illness. This can only be resolved when a reliable and reproducible method for the diagnosis of adrenocortical insufficiency in critical illness is established.

Two double-blind, placebo-controlled studies and a recent meta-analysis concluded that administration of corticosteroids produced no overall benefit in sepsis and septic shock.32–34 As a result, the use of exogenous corticosteroids in critical illness has declined. It is likely that some critically ill patients who several years ago may have inadvertently received corticosteroid treatment for adrenocortical insufficiency may now not be treated. Although there is still uncertainty about the diagnosis of adrenocortical insufficiency and its relationship with mortality in critical illness, there is evidence to support administration of corticosteroids to critically ill patients with suspected adrenocortical insufficiency. In the study of Sibbald and colleagues, only one of five patients with septic shock and adrenocortical insufficiency survived.7 The survivor was the only patient to have received corticosteroid replacement treatment. Furthermore, corticosteroid supplementation improved short-term outcome in patients with adrenocortical insufficiency in septic shock, although mortality was still greater than in patients without adrenocortical insufficiency.18

Critical care clinicians should remain vigilant to the possibility of adrenocortical insufficiency. Unfortunately, the literature does not offer a clear biochemical definition in critical illness. Even if such a definition was established, the time delay required to perform an ACTH stimulation test and cortisol assays would probably negate its contribution towards making a clinical decision about commencing corticosteroid treatment. Adrenocortical insufficiency is clinically suspected in patients with rapidly escalating inotropic requirements associated with poor haemodynamic responses. In practice it is likely that corticosteroids would be administered before a biochemical diagnosis could be confirmed. Most previous studies have used supra-physiological doses of corticosteroids. The well known risks of this may outweigh the benefits of biochemically correcting adrenocortical insufficiency in critical illness. Administration of physiological doses of corticosteroids (cortisol 30 mg daily for adults),35 aiming for physiological replacement rather than pharmacological treatment, may improve long-term mortality in these patients. Even if physiological doses of corticosteroids prove to be beneficial only transiently in this subset of patients, they may still have a useful role. The resulting improvement in cardiovascular stability in the short-term can only increase the
opportunity for other treatments to correct the underlying pathophysiological chaos in critical illness and hopefully reduce mortality.

We feel it is time for a consensus on the definition of adrenocortical insufficiency in critical illness. A similar consensus has been achieved for other conditions. This would standardize future studies and help in the identification of patients who may benefit from corticosteroid treatment. Double-blind, placebo-controlled studies should follow and answer, once and for all, if replacement therapy in this subset will help in the identification of patients who may benefit from adrenocortical insufficiency when adrenocortical insufficiency is suspected.

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References


2. Duggan M, Browne I, Flynn C. Adrenal failure in the critically ill; measure basal and post-stimulation plasma cortisol concentrations more readily; then, clinicians should: have an increased index of suspicion for diagnosing adrenocortical insufficiency in the critically ill; and consider administration of physiological rather than supra-physiological doses of corticosteroids when adrenocortical insufficiency is suspected.


