Defining normal adrenocortical responses (especially glucocorticoid responses) to various stimuli has been a topic of debate for many years in clinical endocrinology. The current view states that a serum total cortisol concentration of 550 nmol/l (20 μg/dl) or more in response to stimulation with adrenocorticotropic hormone (ACTH) indicates normal adrenal responsiveness and reserve and precludes the requirement for exogenous steroid supplementation. This is generally accepted for both the high-dose (250 μg) and low-dose (1 μg) ACTH stimulation tests, although blood levels of ACTH are significantly above physiological levels for the high-dose (1 000 - 60 000 pg/ml) as opposed to the low-dose (100 - 300 pg/ml) ACTH stimulation test. Despite this, peak cortisol responses to both stimuli are similar in healthy individuals. Slightly different criteria have been proposed for the cortisol response to insulin-induced hypoglycaemia, where a cortisol concentration of 497 nmol/l (18 μg/dl) or more is regarded as normal. Unfortunately, these criteria are not applicable to persons with acute illness, and defining normality in the context of different states of physical illness requires revision of established criteria.

Acute illness influences all endocrine axes. This is perhaps most well known in thyroid function, where non-thyroidal illness has, for many years, been shown to influence thyroid function, predominantly in the peripheral conversion of T4 to T3, but also in T4 secretion rates, abnormal thyrotrophin (TSH) pulses and altered peripheral T3 metabolism. There are many reasons for altered responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis in acute illness. Acute illness impacts on the HPA axis through the effect of cytokines on corticotrophin-releasing hormone (CRH) and ACTH secretion, altered synthesis of cortisol-binding globulin (CBG), altered metabolism of CBG, alteration in the relative amounts of free and bound cortisol and loss of the diurnal rhythm of cortisol secretion. This response by the HPA axis to acute illness is possibly an adaptation that facilitates recovery from the acute insult. The difficulty, however, is in distinguishing adaptive responses from inadequate responses.

Current recommendations in defining adequate adrenal function in acute illness derive largely from outcome studies in septic shock. These and other studies have shown that the HPA axis is activated in acute illness and the degree of activation correlates with the severity of the illness. In an attempt to define this response more accurately, a recent study has shown that free cortisol corresponds to the severity of illness more closely than does total cortisol. This study also reported on a method whereby free cortisol is calculated from total cortisol and CBG measurement and found a close correlation with measured free cortisol. However, the performance of the 250 μg and 1 μg ACTH stimulation tests varies in the presence of acute severe illness – in this setting the 250 μg ACTH stimulation test results in significantly higher cortisol responses than the 1 μg ACTH stimulation test and the 1 μg test is best not used to assess the HPA axis in acute illness.

Most studies have shown that mortality in patients with critical illness is greatest in those who have the lowest and the highest serum cortisol levels. This apparent paradox has been accounted for by the development of acquired glucocorticoid resistance in acute illness, such that even elevated cortisol levels are inadequate at a tissue level. Acquired glucocorticoid resistance in acute severe illness is, however, a poorly described condition, possibly related to altered cleavage of cortisol from CBG binding sites, reduced number and affinity of glucocorticoid receptors and an increase in cortisol to cortisone conversion by cytokine-mediated increased activity of 11β-hydroxysteroid dehydrogenase.

The studies of Annane and colleagues in France have provided much of the data used to define normal and abnormal adrenal responses in the intensive care setting. The first of these studies assessed 28-day mortality in relation to basal and stimulated (250 μg ACTH) total serum cortisol in 189 subjects with septic shock. The highest 28-day mortality occurred in subjects with basal cortisol > 938 nmol/l (34 μg/dl) and a maximal cortisol increment in response to 250 μg ACTH injection (Δmax) of < 248 nmol/l (9 μg/dl). In this group, mortality was 80%. Lowest mortality (28%) was seen in the group in whom basal cortisol was ≤ 938 nmol/l and Δmax > 248 nmol/l. Intermediate mortality (67%) occurred in the subjects in whom basal cortisol was ≤ 938 nmol/l and Δmax ≤ 248 nmol/l or basal cortisol > 938 nmol/l and Δmax > 248 nmol/l.

The second study then assessed the influence of low-dose hydrocortisone and fludrocortisone therapy in subjects with septic shock, in relation to the Δmax serum cortisol response to a 250 μg ACTH stimulation test.
test, performed at baseline. Among the subjects with a \( \Delta_{\text{max}} \) cortisol \(< 248 \text{ nmol/l (9 μg/dl)} \), termed the ‘non-responders’, there was a significant reduction in 28-day mortality in those treated with hydrocortisone 50 mg 6-hourly by intravenous injection and fludrocortisone 50 μg daily by nasogastric tube, for 7 days, compared with those given placebo.

Recommendations for glucocorticoid therapy in the context of critical illness, in particular septic shock, have therefore been proposed, based largely on these two studies. One algorithm proposes glucocorticoid therapy for all subjects with critical illness and a random basal serum cortisol below 414 nmol/l (15 μg/dl) or above 938 nmol/l (34 μg/dl) and for those in whom there is a \( \Delta_{\text{max}} \) cortisol response to 250 μg ACTH of \(< 248 \text{ nmol/l (9 μg/dl)} \).\(^3\) This means that almost all persons admitted to an ICU will be required to undergo an ACTH stimulation test on admission.

Despite these recommendations, there remain unanswered questions:

- Do these criteria apply to acute illnesses of lesser severity, or non-medical conditions, such as trauma?
- What is the optimal dose and duration of glucocorticoid replacement and should this vary according to illness severity?
- Is there a means of differentiating acquired glucocorticoid resistance from exaggerated cortisol secretion (such as by differences in ACTH levels)?

It is clear that further studies are required, and one such study appears in this issue of JEMDSA.\(^11\) Venter and colleagues assessed basal and stimulated total cortisol in patients with pulmonary tuberculosis, twice over 5 days, while antituberculosis therapy was initiated. The criterion for normal responsiveness was a \( \Delta_{\text{max}} \) cortisol of 250 nmol/l or more in response to 250 μg ACTH injection. While it could be argued that this criterion applies specifically to patients with critical illness in an ICU, there are no better criteria to use.

It is interesting to note that the mean basal cortisol exceeded 938 nmol/l in both groups of patients studied on day 1, but had declined to below 938 nmol/l in both groups by day 5. Does this mean that there was glucocorticoid resistance in these patients or does this imply an inappropriate adrenal response to tuberculous infection? A subnormal cortisol response to ACTH stimulation was found in 40% of the study group on day 1 and this had declined to 20% on day 5. As for the basal cortisol results, the interpretation of these results is difficult in the absence of well-defined criteria in illness other than septic shock. Do these results mean that initiation of antituberculosis therapy rapidly improves adrenal responsiveness and possibly induces regression of a degree of acquired glucocorticoid resistance? Studies to address these specific issues are clearly needed and will, it is hoped, be undertaken in the near future.

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