Anaesth Intensive Care 2010; **38:** 425-436

Review

Relative adrenal insufficiency in the intensive care population; background and critical appraisal of the evidence

J. COHEN*, B. VENKATESH†

Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

SUMMARY

Dysfunction of the hypothalamo-pituitary adrenal axis has become a central feature in descriptions of the pathophysiology of sepsis. However, despite hundreds of published articles including literature reviews and consensus statements, controversy still exists regarding the fundamental nature of the disorder and its relevance to clinical management. Often referred to as 'relative adrenal insufficiency', a recent consensus conference has proposed the alternate term 'critical illness related corticosteroid insufficiency' and suggested diagnostic criteria of a delta serum cortisol of less than 9 μg/l after adrenocorticotrophic hormone administration or a random total cortisol of under 10 μg/l.

This review attempts to establish a critical reappraisal of the evidence for the existence of relative adrenal insufficiency/critical illness related corticosteroid insufficiency in patients with sepsis and examines the background, controversies and possibilities for future research into the condition.

Key Words: adrenal insufficiency, intensive care, critical illness related adrenal insufficiency

Dysfunction of the hypothalamo-pituitary adrenal (HPA) axis has become a central feature in descriptions of the pathophysiology of sepsis. However, despite hundreds of published articles, including literature reviews and consensus statements, controversy still exists regarding the fundamental nature of the disorder and its relevance to clinical management. Often referred to as relative adrenal insufficiency (RAI), a recent consensus conference has proposed the alternate term critical illness related corticosteroid insufficiency and suggested diagnostic criteria of a delta serum cortisol of less than 250 nmol/l (9 μg/dl) after adrenocorticotrophic hormone administration or a random total cortisol of under 276 nmol/l (10 μg/dl)[1].

In this review we attempt to establish a critical reappraisal of the evidence for the existence of RAI/critical illness related corticosteroid insufficiency in patients with critical illness and examine the background, controversies and possibilities for future research into the condition. Cortisol concentrations are presented as both μg/dl and nmol/l; 1 μg/dl=27.6 nmol/l.

PHYSIOLOGY

The HPA axis forms the keystone of the organisms response to stress and its primary output in man is cortisol. There are a variety of stimuli to cortisol secretion, including tissue damage, cytokine release, hypoxia, hypotension and hypoglycaemia. These factors act upon the hypothalamus to favour the release of corticotrophin releasing hormone (CRH) and vasopressin. CRH is synthesised in the hypothalamus and carried to the anterior pituitary in portal blood, where it stimulates the secretion of adrenocorticotrophic hormone (ACTH), which in turn stimulates the release of cortisol, mineralocorticoids (principally aldosterone) and androgens from the adrenal cortex. Corticotrophin releasing hormone is the major (but not the only) regulator of ACTH release and is secreted in response to a normal hypothalamic circadian regulation and various forms of 'stress'. Vasopressin, oxytocin, angiotensin II and beta-adrenergic agents also stimulate ACTH release while somatostatin, beta-endorphin and enkephalin reduce it. Cortisol has a negative feedback on the hypothalamus and pituitary, inhibiting hypothalamic

* M.R.C.P., F.R.C.A., F.J.F.I.C.M., Senior Specialist in Intensive Care.
† M.D., F.J.F.I.C.M, Professor, Department of Intensive Care, Princess Alexandra and Wesley Hospitals, University of Queensland.

Address for correspondence: Dr J. Cohen, jeremy_cohen@health.qld.gov.au

Accepted for publication on January 7, 2010.

CRH release induced by stress and pituitary ACTH release induced by CRH. During periods of stress, trauma or infection, there is an increase in CRH and ACTH secretion and a reduction in the negative feedback effect, resulting in increased cortisol levels, in amounts roughly proportional to the severity of the illness[2-4].

Under normal circumstances, cortisol is secreted in pulses and in a diurnal pattern[5]. The normal daily output of cortisol is 40 to 80 μmol/day (i.e. 15 to 30 mg/day), producing a maximum plasma cortisol level of 110 to 520 nmol/l (4 to 19 μg/dl) at 0800 to 0900 hours, and a minimal cortisol level of less than 140 nmol/l (<5 μg/dl) after midnight.

The majority of circulating cortisol is bound to an alpha-globulin, cortisol-binding globulin (CBG), otherwise known as transcortin. At normal levels of total plasma cortisol (e.g. 375 nmol/l or 13.5 μg/dl), less than 5% exists as free cortisol in the plasma: however, it is this free fraction that is biologically active. In normal subjects CBG can bind approximately 700 nmol/l (25 μg/dl)[6]. At levels greater than this, the increase in plasma cortisol is largely in the unbound fraction. CBG is a substrate for elastase, a polymorphonuclear enzyme that cleaves CBG, markedly decreasing its affinity for cortisol[7]. This enzymatic cleavage results in the liberation of free cortisol at sites of inflammation. Free cortisol passes through cell membranes to bind with the glucocorticoid (GC) receptor, following which the steroid-receptor complex migrates to the nucleus and influences gene transcription[8,9]. There is

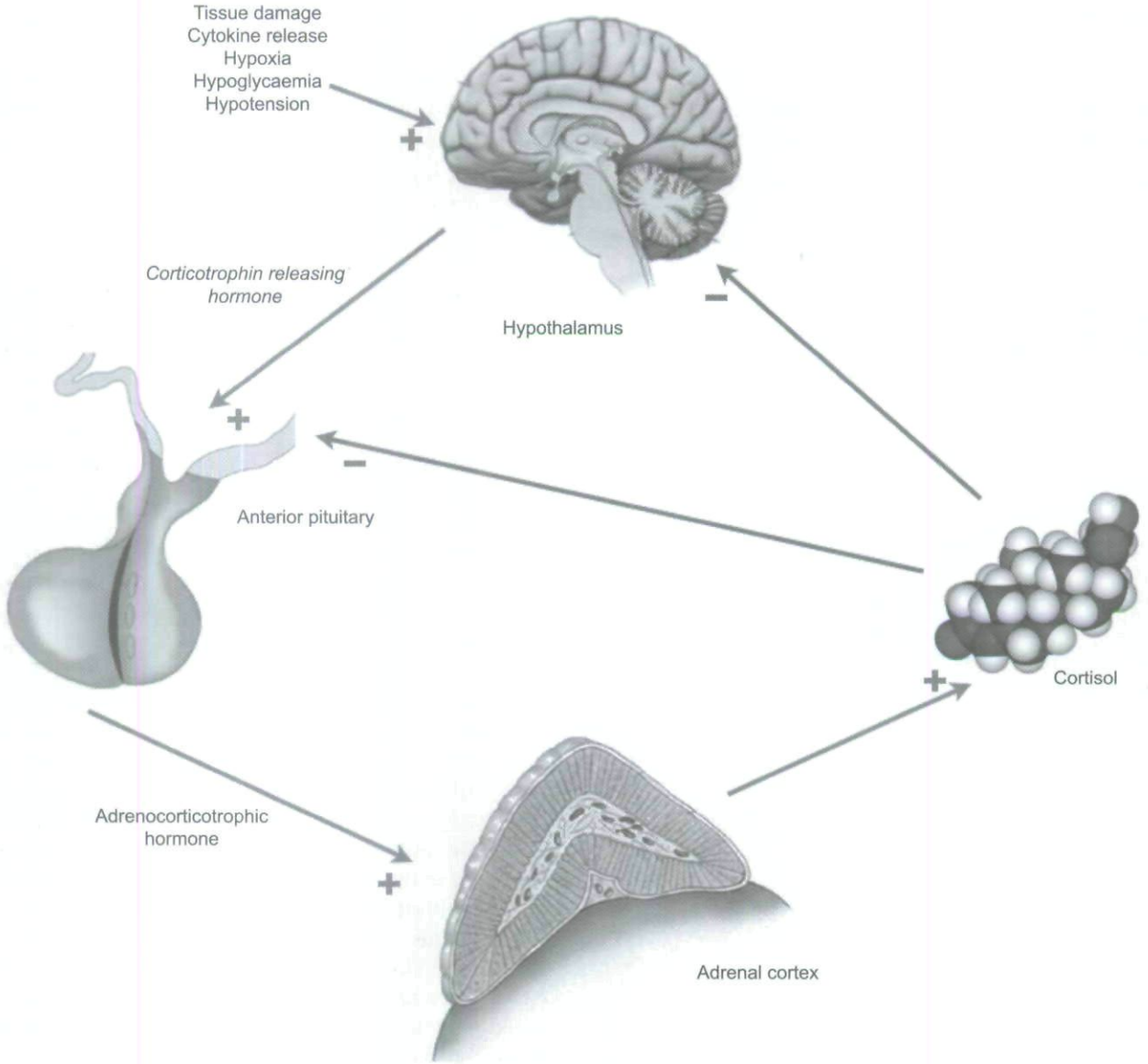

FIGURE 1: The hypothalamo-pituitary adrenal axis.

in addition, accumulating evidence for 'non-genomic' effects of cortisol, in which as yet unidentified membrane receptors may be implicated[10].

The actions of cortisol are pivotal to normal metabolism. It is essential in the maintenance of normal vascular tone, endothelial integrity and potentiates vasoconstrictor action[11]. Its effects upon the immune system are anti-inflammatory and immunosuppressive[12]. The production of cytokines is inhibited, an effect that is mediated via NF-kB[13]. Lymphocyte cell counts decrease, while neutrophil counts rise[12]. While the well-defined effects of cortisol upon the immune system are primarily inhibitory, it is also suggested that normal host defence function requires some cortisol secretion. Cortisol has been described as having a positive effect on immunoglobulin synthesis, potentiation of the acute phase response, wound healing and opsonisation[6].

BACKGROUND

The central role of the HPA axis in the response to stress has now been well characterised. Seyle's observations from the 1940s demonstrated that adrenalectomised animals exposed to shock had a high mortality rate which could be ameliorated by treatment with cortisol. Subsequently it has been confirmed that under conditions of physiological stress there is an increase in ACTH and cortisol secretion, in amounts roughly proportional to the severity of the insult. Surgical procedures such as laparotomy have been observed to increase cortisol concentrations by 84% over the preoperative concentrations, while after less extensive operations such as joint, breast or neck procedures the relative increase is 36%[11]. Patients with a suppressed or non-functional HPA axis have a higher mortality and under conditions of stress require GC supplementation.

The phrase 'relative adrenal insufficiency' appears to have first been proposed by Pollak[14] and adopted by Seyle. Its use in this initial descriptive sense indicated a state in which there has been activation of the adrenal response, but of an inadequate magnitude in proportion to the insult. Several early reports suggested that the outcome from critical illness may be significantly influenced by the presence of RAI. An increase in mortality was observed in the early 1980s following the introduction of etomidate as a sedative agent for critically injured patients. Etomidate is known to impair cortisol synthesis by inhibition of 11-β hydroxylase, and following its use as an infusion in patients with multiple trauma admitted to intensive care, there was an observed increase in mortality from 28 to 77%[15]. This increase resolved once etomidate use was discontinued. At roughly the same time, observations of plasma cortisol measurements on non-selected patients admitted to a general intensive care unit (ICU) suggested that lower plasma cortisol concentrations were associated with a higher mortality[16].

Further reports described critically ill patients with multi-organ failure, in whom the cortisol response following synthetic ACTH administration was reduced: these patients appeared to improve following treatment with GCs[17,18]. Thus, there appeared to be reasonable grounds to suspect that a relative deficiency of cortisol may be influencing the outcome from critical illness and sepsis.

EVIDENCE FOR THE EXISTENCE OF RAI IN CRITICAL ILLNESS

Supporting evidence for the existence of RAI as a clinical entity has primarily come from interpretation of plasma cortisol concentrations, either single plasma measurements or in response to administration of synthetic ACTH. Other clinical signs, such as hyperdynamic shock, abdominal pain, electrolyte disturbances or eosinophilia do not appear to be either specific or sensitive in the setting of critical illness. Many different diagnostic criteria have been proposed, of which the most common suggest either a minimum threshold random cortisol measurement during critical illness or a minimum peak or minimal response in plasma cortisol following a standard corticotropin test (Table 1). However, there are serious limitations to all of these proposed criteria.

RANDOM PLASMA CORTISOL ESTIMATIONS

Critically ill patients are almost uniformly reported to increase their plasma cortisol levels in response to the physiological stress to which they have been exposed. It is considered that endogenous stress is superior to exogenous ACTH administration for the purposes of diagnosing adrenal insufficiency, hence the rationale for using insulin-induced hypoglycaemia as the gold standard investigation[19]. Thus single plasma cortisol estimations performed during periods of severe illness might reasonably be expected to reflect the degree of HPA axis activation. The theory of RAI predicts that in a proportion of patients the elevation of plasma cortisol levels is insufficient for the severity of their illness. This should be expected to manifest as an increase in observable mortality associated with plasma cortisol values at the lower end of the range seen in critical illness.

However, attempts to verify this prediction have not been successful and overall it has not been possible to document a minimum plasma cortisol level below which there is an increase in mortality. Sibbald et al[18] documented a group of five patients with sepsis with a mean cortisol of 380 nmol/l (13.8 μg/dl), of whom four died. Similarly, looking at general ICU patients, Finlay and McKee documented 100% mortality in 36 patients with serum cortisol levels below 350 nmol/l (12.7 μg/dl)[20]. However the majority of other studies have not replicated these findings.

Span and co-workers described 159 critically ill patients with a mean plasma cortisol of 600±280 nmol/l (21.7±10 μg/dl). Non-survivors had significantly higher levels than survivors[21]. Similarly, Jarek et al documented higher cortisol levels in non-survivors of a group of 61 ICU patients[22],

TABLE 1

Study	Population characteristics	Incidence of RAI	Time of assay	Gender ratio (M:F)
Corticotrophin response <250 nmol/l				
Rothwell (1991)	Septic shock	40%	Unknown	1.3:1
Bouachoar (1995)	Septic shock	75%	<24 hours	3.4:1
Annane (2000)	Septic shock	54%	<24 hours	1.6:1
Annane (2002)	Septic shock	76%	<8 hours	2:1
Ho (2006)	Septic shock	33%	<24 hours	1.1:1
Bollaert (2002)	Septic shock	38%	4 days	1.9:1
Siraux (2005)	Septic shock	34%	Unknown	2.4:1
Yildiz (2002)	Sepsis	35%	Unknown	1.5:1
Bourne (2003)	Septic shock	70%	Unknown	Unknown
Sprung (2008)	Septic shock	47%	<72 hours	2:1
Jones (2006)	Septic shock	28%	Unknown	1.7:1
Corticotrophin response <200 nmol/l				
Bouachoar (1995)	Septic shock	68%	<24 hours	3.4:1
Briegel (1996)	Septic shock	50%	Unknown	1.2:1
Oppert (2000)	Septic shock	55%	<72 hours	3:1
Moran (1994)	Septic shock	66%	Unknown	1.5:1
Hatherhill (1999)	Septic shock	52%	Unknown	Unknown
Peak or baseline cortisol criteria				
Peak cortisol <700 nmol/l				
Bourne (2003)	Septic shock	40%	Unknown	Unknown
Peak cortisol <600 nmol/l				
Faber (1993)	Sepsis	20%	<24 hours	1:2.1
Peak cortisol <550 nmol/l				
Bourne (2003)	Septic shock	28%	Unknown	Unknown
Manglik (2003)	Severe sepsis	9%	Unknown	1:1
Peak cortisol <500 nmol/l				
Bouachoar (1995)	Septic shock	6.25%	<24 hours	3.4:1
Soni (1995)	Septic shock	25%	<24 hours	2:1
Marik (2003)	Septic shock	8%	<48 hours	1:1
Baseline cortisol <690 nmol/l				
Marik (2003)	Septic shock	61%	<48 hours	1:1
Baseline cortisol <500 nmol/l				
Moran (1994)	Septic shock	32%	Unknown	1.5:1
Aygen (1997)	Sepsis	16%	<24 hours	1:1.6

RAI = relative adrenal insufficiency, M=male, F=female.

findings reproduced by another study of 70 critically ill patients with basal cortisol values of 1195 nmol/l (43.3 μg/dl) in non-survivors compared to 853 nmol/l (30.9 μg/dl) in survivors (P <0.03)[23]. In a study of 37 patients with sepsis, the median cortisol value was 1399 nmol/l, range 430 to 11040 nmol/l (50.7, 15.6 to 400 μg/dl) with no significant difference between survivors and non-survivors[24]. Likewise, in a study of 32 septic patients, Rothwell et al documented a mean basal cortisol of 728 nmol/l (26.4 μg/dl), which had no impact on mortality. Plasma cortisol was found to have no predictive value in a study of 40 patients with septic shock by Bouachour et al. Basal cortisol concentration was 1015 nmol/l, range 218 to 3118 nmol/l (36.8, 7.9 to 113 μg/dl) and no relationship to outcome could be demonstrated[25]. Drucker et al described a wide range of plasma cortisol in 40 acutely ill patients, of 212 to 8340 nmol/l (7.68 to 302.2 μg/dl), without a correlation with mortality[26]. Additional studies have reported similar results[27,28]. The lack of clear data has resulted in a number of suggested threshold values for random plasma cortisol to diagnose RAI in the critically ill: these vary from 345 to 690 nmol/l (12.5 to 25 μg/dl)[16,25,29-32].

Indeed, when studies comparing plasma cortisol values in survivors and non-survivors are examined, there is a clear trend towards *higher* cortisol values in non-survivors (Figure 2). This observation is the opposite of that predicted by the concept of RAI, namely that non-survivors should have lower cortisol levels.

There are a number of possible explanations for the inability to delineate a minimum threshold total plasma cortisol value in critical illness. First, it appears that there are significant hourly variations in the plasma cortisol concentrations in the critically ill. In a study of 20 septic shock patients performing hourly cortisol measurements, we have demonstrated that total plasma cortisol has such marked variability that a random value has limited diagnostic utility. The individual mean plasma cortisol concentrations ranged from 286±59 nmol/l to 796±83 nmol/l (10.4±2.1 to 28.8±3 μg/dl) with marked hourly variability (CV 8 to 30%). There was no correlation between total plasma cortisol and outcome[33].

Next, it is possible that gender differences may have contributed to the difficulties in analysing the adrenocortical response. In the various septic shock studies, the male:female ratio has varied from 0.8 to 3.4. Available evidence does suggest that gender can influence hormonal response to stress[34,35] and thus may act as a confounding variable. Specifically, males may exhibit an increased sensitivity to GCs following exposure to stress, whereas GC sensitivity decreases in females. Further complicating factors arise from the observation that studies in this area are not uniform with respect to the time period examined. GC concentrations during sepsis have been shown to vary substantially over the time course of the illness. The highest cortisol levels are seen in the early stage of sepsis, with a gradual decline in the later phases[36]. This is illustrated in Figure 3 with data from our own observations of 21 patients in septic shock. Total and free cortisol measurements were performed by mass spectrometry over a time course of 10 days. A review of the published literature shows that patients have been studied

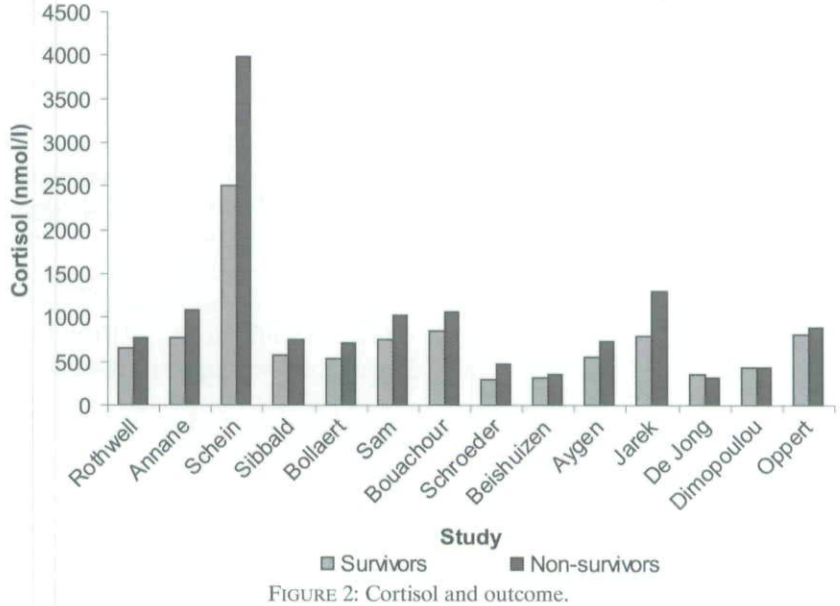

FIGURE 2: Cortisol and outcome.

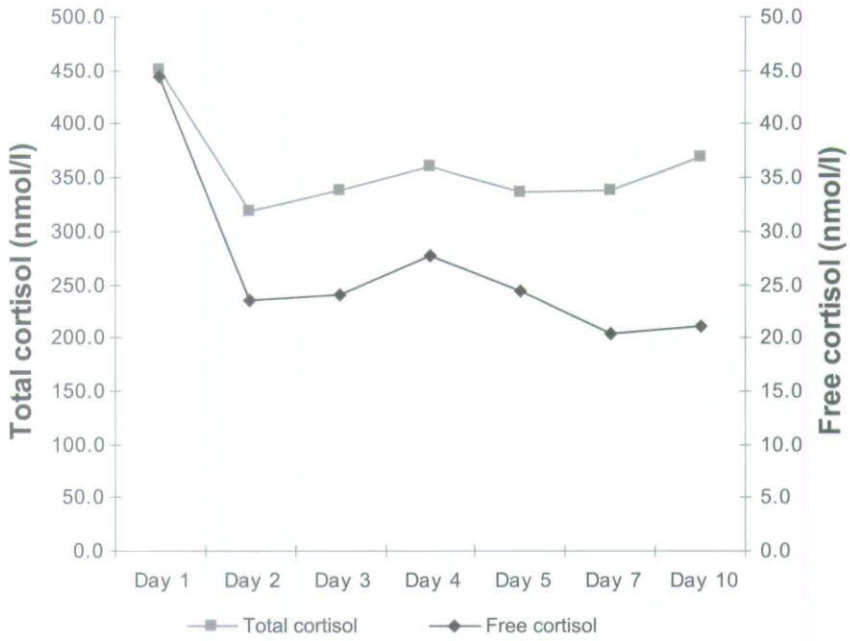

FIGURE 3.

from as early as eight hours within onset of shock and up to 61 days after illness[16] and their data have been pooled together to define optimal adrenal response to critical illness. The former defines the acute adrenal response while the latter identifies the response during chronic critical illness. In some studies, the time from admission to adrenal assessment was not clearly stated[37].

Finally, we have reported that there is a high degree of variability between cortisol assays which may potentially confound the diagnosis of RAI resulting in erroneous labelling of the person's adrenal status[38].

THE CORTICOTROPIN TEST

The failure of random plasma cortisol estimations to provide a correlation with outcome has led to a focus on alternate methods of measuring adrenal insufficiency, of which the standard short corticotropin test has become the most widely used. Originally described in 1965[39], the test comprises the measurement of plasma cortisol concentrations immediately prior to and at 30 and 60 minute intervals after the intravenous administration of 250 μg of 1-24 ACTH. In normal individuals, this stimulus will lead to an increase in serum cortisol to peak concentrations of 500 nmol/l (18 μg/dl) or greater[19]. The test forms part of the standard biochemical investigation of suspected adrenal insufficiency.

The use of the corticotropin test in patients with critical illness has resulted in more consistent correlation with outcome than random plasma cortisol concentrations. Early studies in the area documented an association with a blunted response to cosyntropin with a poor outcome. Rothwell at al described 13 patients with septic shock and elevated basal cortisol, in whom the response to ACTH was less than 250 nmol/l (9 μg/dl); all died[40]. Similarly, in a study examining a population of 26 patients with severe sepsis, five were found to have reduced ACTH responsiveness. All but one of these patients died, the survivor having been treated with pharmacological doses of steroids[18].

In 2000, Annane et al published a large prospective investigation into the response to the standard corticotropin test in patients with septic shock[29]. They described 189 patients with septic shock and detailed a three-level classification system based upon the basal cortisol level and response to ACTH[29]. Mortality was found to be highest in those patients with a basal cortisol level above 938 nmol/l (34 μg/dl) and response to ACTH of less than 248 nmol/l (9 μg/dl). Patients with a basal cortisol above 938 nmol/l (34 μg/dl) but a cortisol response greater than 248 nmol/l (9 μg/dl) did better, while the best prognosis was seen in the group with a lower basal cortisol level and high response to ACTH. Other workers have described similar findings: Moran et al[28] demonstrated that an increase in mortality was predicted by a decreased responsiveness to ACTH; likewise Bollaert et al in a retrospective study of 82 patients with septic shock reported that both high basal cortisol and a poor increment on corticotrophin

administration were independent predictors of mortality[41]. However, not all investigators have been able to replicate these findings[22,25,26] and a number of suggested diagnostic criteria have been published, including a baseline cortisol below 500 nmol/l (18 μg/dl) at any time[42] an absolute rise of less than 200 nmol/l (7 μ/dl) or a peak of less than 550 nmol/l (20 μg/dl)[43], a rise of less than 250 nmol/l (9 μg/dl)[29] and a rise in stimulated cortisol over baseline[25]. A more recent large scale retrospective study[44] evaluated 562 patients with sepsis and determined that incremental response to ACTH stimulation was independently associated with mortality, whereas cortisol levels alone were not. While the controversy related to the diagnostic criteria for adrenal insufficiency is not settled, more recent review articles suggest that a rise in baseline cortisol of less than 250 nmol/l (9 μg/dl) in response to a standard short corticotropin test is diagnostic of adrenal insufficiency in the critically ill[1].

CONTROVERSIES RELATED TO THE CORTICOTROPIN TEST

While it is clear that a reduction in responsiveness to the corticotropin test is associated with a poor outcome in sepsis, the interpretation of this finding is debatable. A primary concern is related to the use of cortisol increment, rather than peak cortisol response as the outcome determinant. The cortisol increment (defined as the peak cortisol concentration at either 30 or 60 minutes subtracted by the baseline) has been shown to be an unreliable index of adrenal function as it may not distinguish normal patients from those with adrenal insufficiency. Speckart et al demonstrated that in a proportion of normal controls, the increment in response to a corticotropin test was less than 200 nmol/l (7 μg/dl), whereas the peak values all exceeded 500 nmol/l (18 μg/dl)[45]. Stewart et al documented that patients with a high basal cortisol may fail to achieve a cortisol rise in response to a stimulation test but would not necessarily fail an insulin tolerance test[46]. Widmer et al also demonstrated that in a third of healthy unstressed controls a cortisol increment of over 250 nmol/l (9 μg/dl) was not reached, despite all the patients reaching peak cortisol concentrations of over 500 nmol/l (18 μg/dl)[47]. It is also likely that pre-existing high circulating ACTH levels may suppress the cortisol response; Arvat et al examined the effect of repeated corticotropin administration on 12 healthy volunteers and demonstrated that the response to ACTH was inversely related to the dose of the previous challenge[48], speculating that this may represent either exhaustion of adrenal reserve or a self-protective mechanism against adrenal over-stimulation. This may be an important mechanism in sepsis due to high circulating ACTH levels[49]. The lack of a pre-defined peak cortisol as a index of adequate adrenal response in this setting leads to what may appear to be a biologically implausible scenario: a patient with a high peak cortisol but reduced cortisol increment may be defined as suffering from adrenal insufficiency, whereas one with an adequate increment but substantially lower peak cortisol may not. This apparent contradiction has led to the suggestion that high circulating cortisol concentrations in this setting represent evidence of tissue GC resistance, a subject we address in a subsequent section.

The lack of biological robustness of the cortisol increment as an index of adrenal insufficiency raises perhaps the most important question with respect to its validity; that is, is it truly a modifiable risk factor or merely a marker of severity of injury? The issue is central to the concept of adrenal insufficiency in the critically ill, but is clearly a difficult one to address. The pattern of a reduced cortisol increment can be observed in a number of other conditions apart from sepsis: these include head injury[50], trauma[51] and burns[52], which may suggest that it is a general response to critical illness. At present the evidence that treating patients with septic shock and a reduced cortisol increment results in an improved outcome is contradictory. The 2002 study by Annane et al suggested an improved outcome in these patients, whereas the CORTICUS study was not able to replicate these findings[53,54].

There are further controversies which relate to the conduct and interpretation of the corticotropin test. The standard 250 μg dose can result in circulating concentrations of ACTH as high as 60,000 pg/ml, which are far higher than those normally observed during stress[31]. A low dose regimen, using 1 μg of ACTH has therefore been advocated, with evidence that it is more sensitive and specific for the diagnosis of adrenal insufficiency[55]. However, most of this data has been collected from the non-critically ill population. Marik et al compared the high dose and low dose tests in a population of septic patients[31]. Using the haemodynamic response to corticosteroids as a gold standard for the diagnosis of adrenal insufficiency, they determined the sensitivity of the low dose test as 62%, compared to that of the high dose test as 29%. However, as discussed earlier, a gold standard for diagnosis has not been generally agreed upon and the relative lack of data on the low dose test in the critically ill population has meant it has not yet gained widespread support[30].

ALTERNATIVE METHODS TO ASSESS ADRENAL INSUFFICIENCY IN THE CRITICALLY ILL

Given the difficulties associated with random cortisol estimation and the corticotropin test, alternative diagnostic strategies have been examined. These include estimation of free cortisol, use of the metyrapone test and the clinical response to GC administration.

The majority of circulating cortisol (90%) is bound to CBG and it is only the free fraction that possesses biological activity. During critical illness, levels of cortisol binding globulin decrease[49] and free cortisol levels may increase secondary to the cleavage of cortisol binding globulin by neutrophil elastase. However, commercial assays only measure the total plasma cortisol, so a physiologically significant rise in free cortisol would be missed.

Free cortisol levels in intensive care patients have been examined in a recent study[56] which demonstrated that in patients with hypoproteinemia, serum total cortisol levels were reduced, whereas the serum free cortisol levels were in fact elevated. Another study, examining patients with sepsis and septic shock, suggested that free cortisol correlated with sickness severity more closely than did total cortisol[57]. However, the superiority of free cortisol estimation over total cortisol is by no means clear. A prospective examination of 125 patients with sepsis or septic shock failed to demonstrate any advantage of free cortisol as a predictor of outcome[58] and an investigation into 278 patients presenting with community-acquired pneumonia produced similar results[59]. Free cortisol estimations are not yet widely available, thus limiting the potential usefulness of the test. There is however, evidence that calculation of the free cortisol index, from measurement of either CBG or albumin, correlates reasonably well with measured free cortisol values[57,60].

The metyrapone test was initially developed as a test of pituitary reserve[61]. Metyrapone inhibits the adrenal enzyme 11-β hydroxylase which converts 11-desoxycortisol to cortisol. When given to subjects with normal adrenal function the decline in serum cortisol concentration stimulates ACTH production, leading to an increase in adrenal steroidogenesis proximal to the site of enzyme blockade and a subsequent accumulation of 11-desoxycortisol.

Annane et al studied the effect of performing a metyrapone test on 101 patients with sepsis[62]. Adrenal insufficiency was diagnosed in 60% of patients on the basis of inadequate rise in 11-desoxycortisol and in 32% of patients on the basis of a corticotropin test. The authors concluded the metyrapone testing may be a useful adjunct to diagnosing adrenal insufficiency in this patient group.

Administration of hydrocortisone has been shown to decrease the time to shock reversal in vasopressor-dependent patients with sepsis[63,64], which has led to the suggestion that this response may be used as a clinical index of adrenal insufficiency[31]. However, while some studies have suggested that plasma cortisol concentrations may predict those patients who exhibit a haemodynamic response to GC treatment[65,66], others have failed to demonstrate this effect[63,67]. In the large scale CORTICUS trial, patients designated as responding to a corticotropin test had a faster rate of shock reversal, but this was not associated with a survival benefit and the total numbers of patients who underwent reversal of shock was not affected by hydrocortisone treatment. The authors speculated that these findings may be unrelated to adrenal insufficiency[54].

TISSUE GLUCOCORTICOID RESISTANCE

More recently it has been suggested that peripheral tissue resistance to glucocorticoid activity may play an important role in the HPA axis response to critical illness[1]. Peripheral GC resistance has been described in a number of chronic inflammatory conditions, including asthma, rheumatoid arthritis and inflammatory bowel disease[68]. This is a plausible mechanism which may partly explain the observed difficulties in assessing adrenal function using plasma cortisol concentrations in this group. However, while it is apparent that there are a number of changes in GC metabolism that occur at the cellular level in patients with sepsis, the clinical relevance of these changes is not yet clear.

Glucocorticoids, of which cortisol is the primary example in man, circulate in both bound and free forms. At normal levels of circulating cortisol, the majority (over 95%) is bound to an α_2-globulin, CBG, with a small fraction bound to albumin. The remainder circulates as a free fraction and it is this portion that exerts biological activity. Free plasma cortisol passes from the plasma to the interstitium and then through the cell membrane where it binds to the intracellular GC receptor.

The interstitial cortisol concentration thus represents the available GC pool which is able to enter the cell and bind to the GC receptor. As such, it may be a more accurate marker of tissue cortisol activity than plasma concentrations. However, the reference range for interstitial cortisol in the critically ill patient is unknown. It has historically been assumed that total plasma cortisol concentrations determine free plasma cortisol concentrations which

in turn determine interstitial cortisol concentrations; the so called 'cortisol cascade'. However, microdialysis studies examining antibiotic concentrations have demonstrated that tissue and interstitial levels may be significantly dissociated[69]. A number of factors may lead to similar dissociations between plasma and interstitial cortisol concentrations. Cortisol can be cleaved from cortisol-binding globulin by the actions of neutrophil elastase, an enzyme released from polymorphonuclear leukocytes at the site of inflammation[7]. The extensive inflammatory response noted in sepsis may therefore lead to an increased interstitial cortisol concentrations via this mechanism. Additionally, intracellular cortisol, generated from cortisone secondary to the activity of 11-betahydroxysteroid dehydrogenase 1 enzyme, can diffuse into the interstitium[70], thus contributing to the interstitial pool of free cortisol.

Other factors may influence interstitial cortisol concentrations. These include interstitial fluid volume, capillary "leakage" and peripheral tissue perfusion, all of which are likely to be significantly abnormal in patients with critical illness. To date there are no experimental data examining interstitial cortisol concentrations in critical illness. We have recently completed a pilot study into the feasibility of measuring interstitial cortisol concentrations in patients with severe burn injury using a microdialysis technique[71]. Our preliminary findings suggest that interstitial cortisol concentrations are elevated in this patient group and are poorly correlated with the free plasma concentrations.

Following its passage into the cell, cortisol is subject to the actions of the 11-β hydroxysteroid dehydrogenase (11-β HSD) enzyme system. This widely distributed intracellular system exists as two isomers; 11-β HSD 1 is primarily reductase and generates cortisol from inactive cortisone, whereas 11-β HSD 2 is a dehydrogenase and inactivates cortisol by converting it to cortisone[72]. The relative activity of these isomers thus has a profound effect upon intracellular cortisol levels, which will be tissue specific.

The HSD system has been the subject of intense investigation in recent years and it has become apparent that it has a central role in the control of GC metabolism. Abnormalities of the system have been implicated in the pathogenesis of obesity, hypertension and the metabolic syndrome[73]. Genetically modified mice with excess 11-β HSD 1 production develop obesity, hypertension and dyslipidaemia; similarly knockout 11-β HSD 1 mice are resistant to these conditions. However, despite the large research interest in this field, very few studies have examined the role of the 11-β HSD system in critical illness. We have recently published data showing the plasma cortisol to cortisone ratio, an index of total body HSD activity, is increased in critically ill patients with sepsis and trauma[74]. This is suggestive of increased 11-β HSD 1 activity, which would lead to an increase in intracellular cortisol generation. This observation is consistent with other lines of evidence demonstrating similar elevations of cortisol: cortisone ratio in general and postoperative hospital patients[75,76], and in vitro studies revealing up regulation of 11-β HSD 1 gene expression after exposure to pro-inflammatory cytokines[77]. We have recently observed a similar increase in 11-β HSD 1 expression in hepatic and adipose tissue from rats undergoing a caecal perforation model (paper in preparation).

Glucocorticoid action is mediated through the GC receptor, a cytosolic protein that is part of the nuclear hormone receptor superfamily. Prior to binding to GC, the cytoplasmic GR forms a multiprotein complex with several proteins, including heat shock proteins, co-chaperones and various protein kinases. Binding of GC to the ligand domain of the receptor results in dissociation from the multiprotein complex and translocation of the receptor-ligand complex into the cell nucleus. Translocation occurs within 30 minutes of exposure of the cell to GC and results in binding to specific DNA binding sites termed GC response elements. GC response elements can have positive or negative effects on transcription, affecting an estimated 2000 genes. The GC receptor also directly interacts with a number of other transcription factors, including the pro-inflammatory nuclear factor κB.

GR expression and transcription appears to be significantly changed in sepsis and critical illness, with the preponderance of evidence suggesting a decrease in GR function. Pariante and co-workers demonstrated that interleukin-1α reduced GR translocation and GR mediated gene transcription in mouse fibroblast cell line[78], while TNFα has also been shown to impair GR mediated transcription[79]. GC receptor binding has been show to be reduced in experimental models of sepsis in dogs[80], rats exposed to thermal injury[81] and in leucocytes of patients with sepsis[82]. However, a study of skeletal muscle in rats suggested an increase in GR expression and function[83]. In a recent study carried out in guinea pigs, sepsis induced by lipopolysaccharide reduced GR expression in lung, kidney and spleen tissue. In contrast, NF- κB translocation to the nucleus and binding activity was significantly increased[84].

These results would seem to indicate that significant changes occur in tissue GC metabolism during sepsis and septic shock, but the overall clinical relevance of these changes is still unclear. Decreases in GC receptor expression and activity need to be interpreted in the setting of increased intracellular cortisol availability, and there are no data that relate indices of tissue GC activity to outcome in critically ill patients.

SUMMARY

The concept of relative adrenal insufficiency, or critical illness corticosteroid insufficiency, has caused a great deal of debate. Our assertion is that the evidence to support its existence as a relevant clinical entity is currently not compelling. The hypothesis predicts that patients with random plasma cortisol concentrations below the diagnostic threshold would have worse outcomes but data from multiple studies do not demonstrate this relationship. The corticotropin test can be shown to correlate with outcome but the cortisol increment is not a reliable marker of adrenal insufficiency, and there is no convincing evidence to suggest it is any more than an indicator of illness severity. The concept of tissue GC resistance in critical illness is highly plausible; however, there is as yet no gold standard method for measuring tissue activity and no available data on its relationship to clinical outcomes. We therefore suggest that the terms 'RAI' and 'critical illness related corticosteroid insufficiency' be abandoned and that routine testing of adrenal function in critically ill patients is unnecessary. For patients who are suspected of having Addison's disease, standard endocrinological diagnostic criteria should be used. If further research leads to accurately identifying patients who manifest tissue GC resistance, a targeted trial of GC therapy in this group may well be indicated.

REFERENCES

1. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008; 36:1937-1949.
2. Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab 1991; 72:39-45.
3. Barton RN, Stoner HB, Watson SM. Relationships among plasma cortisol, adrenocorticotrophin, and severity of injury in recently injured patients. J Trauma 1987; 27:384-392.
4. Chernow B, Alexander HR, Smallridge RC, Thompson WR, Cook D, Beardsley D et al. Hormonal responses to graded surgical stress. Arch Intern Med 1987; 147:1273-1278.
5. Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. J Clin Endocrinol Metab 1971; 33:14-22.
6. Burchard K. A review of the adrenal cortex and severe inflammation: quest of the "eucorticoid" state. J Trauma 2001; 51:800-814.
7. Pemberton PA, Stein PE, Pepys MB, Potter JM, Carrell RW. Hormone binding globulins undergo serpin conformational change in inflammation. Nature 1988; 336:257-258.
8. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995; 332:1351-1362.
9. Weinberger C, Hollenberg SM, Rosenfeld MG, Evans RM. Domain structure of human glucocorticoid receptor and its relationship to the v-erb-A oncogene product. Nature 1985; 318:670-672.
10. Iwasaki Y, Aoki Y, Katahira M, Oiso Y, Saito H. Non-genomic mechanisms of glucocorticoid inhibition of adrenocorticotropin secretion: possible involvement of GTP-binding protein. Biochem Biophys Res Commun 1997; 235:295-299.
11. Lamberts SW, Bruining HA, de Jong FH. Corticosteroid therapy in severe illness. N Engl J Med 1997; 337:1285-1292.
12. Larsen P, Kronenburg H, Melmed S, Polonsky K. Williams Textbook of Endocrinology. Saunders, Elsevier 2003.
13. Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. Annu Rev Immunol 2002; 20:125-163.
14. Pollak H. Wound shock and suprarenal cortex. Lancet 1940; 235:574-575.
15. Watt I, Ledingham IM. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. Anaesthesia 1984; 39:973-981.
16. Finlay WE, McKee JI. Serum cortisol levels in severely stressed patients. Lancet 1982; 1:1414-1415.
17. Baldwin WA, Allo M. Occult hypoadrenalism in critically ill patients. Arch Surg 1993; 128:673-676.
18. Sibbald WJ, Short A, Cohen MP, Wilson RF. Variations in adrenocortical responsiveness during severe bacterial infections. Unrecognized adrenocortical insufficiency in severe bacterial infections. Ann Surg 1977; 186:29-33.
19. Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003; 361:1881-1893.
20. McKee JI, Finlay WE. Cortisol replacement in severely stressed patients. Lancet 1983; 1:484.
21. Span LF, Hermus AR, Bartelink AK, Hoitsma AJ, Gimbrere JS, Smals AG et al. Adrenocortical function: an indicator of severity of disease and survival in chronic critically ill patients. Intensive Care Med 1992; 18:93-96.
22. Jarek MJ, Legare EJ, McDermott MT, Merenich JA, Kollef MH. Endocrine profiles for outcome prediction from the intensive care unit. Crit Care Med 1993; 21:543-550.
23. Jurney TH, Cockrell JL Jr, Lindberg JS, Lamiell JM, Wade CE. Spectrum of serum cortisol response to ACTH in ICU patients. Correlation with degree of illness and mortality. Chest 1987; 92:292-295.
24. Schein RM, Sprung CL, Marcial E, Napolitano L, Chernow B. Plasma cortisol levels in patients with septic shock. Crit Care Med 1990; 18:259-263.
25. Bouachour G, Tirot P, Gouello JP, Mathieu E, Vincent JF, Alquier P. Adrenocortical function during septic shock. Intensive Care Med 1995; 21:57-62.

26. Drucker D, Shandling M. Variable adrenocortical function in acute medical illness. Crit Care Med 1985; 13:477-479.
27. Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME. Cortisol levels and mortality in severe sepsis. Clin Endocrinol (Oxf) 2004; 60:29-35.
28. Moran JL, Chapman MJ, O'Fathartaigh MS, Peisach AR, Pannall PR, Leppard P. Hypocortisolaemia and adrenocortical responsiveness at onset of septic shock. Intensive Care Med 1994; 20:489-495.
29. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 2000; 283:1038-1045.
30. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003; 348:727-734.
31. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. Crit Care Med 2003; 31:141-145.
32. Zaloga GP, Marik P. Hypothalamic-pituitary-adrenal insufficiency. Crit Care Clin 2001; 17:25-41.
33. Venkatesh B, Mortimer RH, Couchman B, Hall J. Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. Anaesth Intensive Care 2005; 33:201-209.
34. Puder JJ, Freda PU, Goland RS, Wardlaw SL. Estrogen modulates the hypothalamic-pituitary-adrenal and inflammatory cytokine responses to endotoxin in women. J Clin Endocrinol Metab 2001; 86:2403-2408.
35. Rohleder N, Schommer NC, Hellhammer DH, Engel R, Kirschbaum C. Sex differences in glucocorticoid sensitivity of proinflammatory cytokine production after psychosocial stress. Psychosom Med 2001; 63:966-972.
36. Marx C, Petros S, Bornstein SR, Weise M, Wendt M, Menschikowski M et al. Adrenocortical hormones in survivors and nonsurvivors of severe sepsis: diverse time course of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, and cortisol. Crit Care Med 2003; 31:1382-1388.
37. Schroeder S, Wichers M, Klingmuller D, Hofer M, Lehmann LE, von Spiegel T et al. The hypothalamic-pituitary-adrenal axis of patients with severe sepsis: altered response to corticotropin-releasing hormone. Crit Care Med 2001; 29:310-316.
38. Cohen J, Ward G, Prins J, Jones M, Venkatesh B. Variability of cortisol assays can confound the diagnosis of adrenal insufficiency in the critically ill population. Intensive Care Med 2006; 32:1901-1905.
39. Wood JB, Frankland AW, James VH, Landon J. A rapid test of adreocortical function. Lancet 1965; 1:243-245.
40. Rothwell PM, Udwadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. Lancet 1991; 337:582-583.
41. Bollaert P-E, Fieux F, Charpentier C, Levy B. Baseline cortisol levels, cortisol response to corticotropin, and prognosis in late septic shock. Shock 2003; 19:13-15.
42. Aygen B, Inan M, Doganay M, Kelestimur F. Adrenal functions in patients with sepsis. Exp Clin Endocrinol Diabetes 1997; 105:182-186.
43. Briegel J, Schelling G, Haller M, Mraz W, Forst H, Peter K. A comparison of the adrenocortical response during septic shock and after complete recovery. Intensive Care Med 1996; 22:894-899.
44. Lipiner-Friedman D, Sprung CL, Laterre PF, Weiss Y, Goodman SV, Vogeser M et al. Adrenal function in sepsis: the retrospective Corticus cohort study. Crit Care Med 2007; 35:1012-1018.
45. Speckart PF, Nicoloff JT, Bethune JE. Screening for adrenocortical insufficiency with cosyntropin (synthetic ACTH). Arch Intern Med 1971; 128:761-763.
46. Stewart PM, Corrie J, Seckl JR, Edwards CR, Padfield PL. A rational approach for assessing the hypothalamo-pituitary-adrenal axis. Lancet 1988; 1:1208-1210.
47. Widmer IE, Puder JJ, Konig C, Pargger H, Zerkowski HR, Girard J et al. Cortisol response in relation to the severity of stress and illness. J Clin Endocrinol Metab 2005; 90:4579-4586.
48. Arvat E, Di Vito L, Lanfranco F, Maccario M, Baffoni C, Rossetto R et al. Stimulatory effect of adrenocorticotropin on cortisol, aldosterone, and dehydroepiandrosterone secretion in normal humans: dose-response study. J Clin Endocrinol Metab 2000; 85:3141-3146.
49. Beishuizen A, Thijs LG, Vermes I. Patterns of corticosteroid-binding globulin and the free cortisol index during septic shock and multitrauma. Intensive Care Med 2001; 27:1584-1591.
50. Dimopoulou I, Tsagarakis S, Douka E, Zervou M, Kouyialis AT, Dafni U et al. The low-dose corticotropin stimulation test in acute traumatic and non-traumatic brain injury: incidence of hypo-responsiveness and relationship to outcome. Intensive Care Med 2004; 30:1216-1219.
51. Guillamondegui OD, Gunter OL, Patel S, Fleming S, Cotton BA, Morris JA Jr. Acute adrenal insufficiency may affect outcome in the trauma patient. Am Surg 2009; 75:287-290.
52. Reiff DA, Harkins CL, McGwin G Jr, Cross JM, Rue LW. Risk factors associated with adrenal insufficiency in severely injured burn patients. J Burn Care Res 2007; 28:854-858.
53. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288:862-871.
54. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008; 358:111-124.
55. Dickstein G, Shechner C, Nicholson WE, Rosner I, Shen-Orr Z, Adawi F et al. Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test. J Clin Endocrinol Metab 1991; 72:773-778.
56. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. N Engl J Med 2004; 350:1629-1638.
57. Ho JT, Al-Musalhi H, Chapman MJ, Quach T, Thomas PD, Bagley CJ. Septic shock and sepsis: a comparison of total and free plasma cortisol levels. J Clin Endocrinol Metab 2006; 91:105-114.
58. Bendel S, Karlsson S, Pettila V, Loisa P, Varpula M, Ruokonen E. Free cortisol in sepsis and septic shock. Anesth Analg 2008; 106:1813-1819.
59. Christ-Crain M, Stolz D, Jutla S, Couppis O, Muller C, Bingisser R. Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. Am J Respir Crit Care Med 2007; 176:913-920.
60. le Roux CW, Chapman GA, Kong WM, Dhillo WS, Jones J, Alaghband-Zadeh J. Free cortisol index is better than serum total cortisol in determining hypothalamic-pituitary-adrenal status in patients undergoing surgery. J Clin Endocrinol Metab 2003; 88:2045-2048.
61. Liddle GW, Estep HL, Kendall JW Jr, Williams WC Jr, Townes AW. Clinical application of a new test of pituitary reserve. J Clin Endocrinol Metab 1959; 19:875-894.
62. Annane D, Maxime V, Ibrahim F, Alvarez JC, Abe E, Boudou P. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. Am J Respir Crit Care Med 2006; 174:1319-1326.

63. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 1998; 26:645-650.
64. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med 1999; 27:723-732.
65. Annane D, Bellissant E, Sebille V, Lesieur O, Mathieu B, Raphael JC et al. Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. Br J Clin Pharmacol 1998; 46:589-597.
66. Oppert M, Reinicke A, Graf KJ, Barckow D, Frei U, Eckardt KU. Plasma cortisol levels before and during "low-dose" hydrocortisone therapy and their relationship to hemodynamic improvement in patients with septic shock. Intensive Care Med 2000; 26:1747-1755.
67. Morel J, Venet C, Donati Y, Charier D, Liotier J, Frere-Meunier D et al. Adrenal axis function does not appear to be associated with hemodynamic improvement in septic shock patients systematically receiving glucocorticoid therapy. Intensive Care Med 2006; 32:1184-1190.
68. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. Lancet 2009; 373:1905-1907.
69. Dalley AJ, Lipman J, Deans R, Venkatesh B, Rudd M, Roberts MS et al. Tissue accumulation of cephalothin in burns: a comparative study by microdialysis of subcutaneous interstitial fluid cephalothin concentrations in burn patients and healthy volunteers. Antimicrob Agents Chemother 2009; 53:210-215.
70. Sandeep TC, Andrew R, Homer NZ, Andrews RC, Smith K, Walker BR. Increased in vivo regeneration of cortisol in adipose tissue in human obesity and effects of the 11beta-hydroxysteroid dehydrogenase type 1 inhibitor carbenoxolone. Diabetes 2005; 54:872-879.
71. Cohen J, Deans R, Dalley A, Lipman J, Roberts MS, Venkatesh B. Measurement of tissue cortisol levels in patients with severe burns: a preliminary investigation. Crit Care 2009; 13:R189.
72. Tomlinson JW, Stewart PM. Cortisol metabolism and the role of 11beta-hydroxysteroid dehydrogenase. Best Pract Res Clin Endocrinol Metab 2001; 15:61-78.
73. Tomlinson JW, Walker EA, Bujalska IJ, Draper N, Lavery GG, Cooper MS et al. 11beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. Endocr Rev 2004; 25:831-866.
74. Venkatesh B, Cohen J, Hickman I, Nisbet J, Thomas P, Ward G et al. Evidence of altered cortisol metabolism in critically ill patients: a prospective study. Intensive Care Med 2007; 33:1746-1753.
75. Vogeser M, Groetzner J, Kupper C, Briegel J. The serum cortisol:cortisone ratio in the postoperative acute-phase response. Horm Res 2003; 59:293-296.
76. Vogeser M, Zachoval R, Felbinger TW, Jacob K. Increased ratio of serum cortisol to cortisone in acute-phase response. Horm Res 2002; 58:172-175.
77. Cai TQ, Wong B, Mundt SS, Thieringer R, Wright SD, Hermanowski-Vosatka A. Induction of 11beta-hydroxysteroid dehydrogenase type 1 but not -2 in human aortic smooth muscle cells by inflammatory stimuli. J Steroid Biochem Mol Biol 2001; 77:117-122.
78. Pariante CM, Pearce BD, Pisell TL, Sanchez CI, Po C, Su C et al. The proinflammatory cytokine, interleukin-1alpha, reduces glucocorticoid receptor translocation and function. Endocrinology 1999; 140:4359-4366.
79. Kino T, Chrousos GP. Tumor necrosis factor alpha receptor- and Fas-associated FLASH inhibit transcriptional activity of the glucocorticoid receptor by binding to and interfering with its interaction with p160 type nuclear receptor coactivators. J Biol Chem 2003; 278:3023-3029.
80. Li F, Xu RB. Changes in canine leukocyte glucocorticoid receptors during endotoxin shock. Circ Shock 1988; 26:99-105.
81. Liu DH, Su YP, Zhang W, Lu SF, Ran XZ, Gao JS et al. Changes in glucocorticoid and mineralocorticoid receptors of liver and kidney cytosols after pathologic stress and its regulation in rats. Crit Care Med 2002; 30:623-627.
82. Molijn GJ, Koper JW, van Uffelen CJ, de Jong FH, Brinkmann AO, Bruining HA et al. Temperature-induced down-regulation of the glucocorticoid receptor in peripheral blood mononuclear leucocyte in patients with sepsis or septic shock. Clin Endocrinol (Oxf) 1995; 43:197-203.
83. Sun X, Fischer DR, Pritts TA, Wray CJ, Hasselgren PO. Expression and binding activity of the glucocorticoid receptor are upregulated in septic muscle. Am J Physiol Regul Integr Comp Physiol 2002; 282:R509-518.
84. Kamiyama K, Matsuda N, Yamamoto S, Takano K, Takano Y, Yamazaki H et al. Modulation of glucocorticoid receptor expression, inflammation, and cell apoptosis in septic guinea pig lungs using methylprednisolone. Am J Physiol Lung Cell Mol Physiol 2008; 295:L998-1006.