Adrenal Insufficiency in Critical Illness

Mark Stuart Cooper, BM BCh, MRCP, PhD
Paul Michael Stewart, MD, FRCP, FmedSci

One of the more controversial areas in critical care in recent decades relates to the issue of adrenal insufficiency and its treatment in critically ill patients. There is no consensus on which patients to test for adrenal insufficiency, which tests to use and how to interpret them, whether to use corticosteroids, and, if so, who to treat and with what dose. This review illustrates the complexity and diversity of pathophysiological changes in glucocorticoid secretion, metabolism, and action and how these are affected by various types of illness. It will review adrenal function testing and give guidance on corticosteroid replacement regimens based on current published literature. There remain inherent difficulties in interpreting the effects of glucocorticoid replacement during critical illness because of the diversity of effects of glucocorticoids on various tissues. Investigation and treatment will depend on whether the likely cause of corticosteroid insufficiency is adrenal or central in origin.

Key words: *corticosteroids, hydrocortisone, cortisol, sepsis, adrenal insufficiency, Addison's disease*

One of the more controversial areas in critical care in recent decades relates to the issue of adrenal insufficiency in critically ill patients and whether these patients should receive glucocorticoid therapy. Although this subject has been discussed in recent reviews [1-5], there is currently no consensus on which patients to test for adrenal insufficiency, which tests to use and how to interpret them, whether glucocorticoids are beneficial, and, if so, who should be treated and with what dose. This review illustrates the complexity and diversity of physiological and pathological changes in glucocorticoid secretion, metabolism, and action and how these changes will be affected by various types of illness. We will illustrate adrenal function testing and how interpretation of these tests will depend on the underlying illness being treated. There are inherent difficulties in interpreting the effects of glucocorticoid replacement during critical illness, including the diversity of effects of glucocorticoids on various tissues. We offer advice as to when glucocorticoids should be given on the basis of the available evidence.

From the Department of Endocrinology, Division of Medical Sciences, Institute of Biomedical Research, The University of Birmingham, United Kingdom.

Received October 3, 2006. Accepted for publication December 18, 2006.

Address correspondence to Mark Stuart Cooper, BM BCh, MRCP, PhD, Department of Endocrinology, Division of Medical Sciences, Institute of Biomedical Research, The University of Birmingham, Birmingham B15 2TT, United Kingdom, e-mail: m.s.cooper@bham.ac.uk.

Cooper MS, Stewart PM. Adrenal insufficiency in critical illness. *J Intensive Care Med*. 2007;22:348-362.

DOI: 10.1177/0885066607307832

Corticosteroid Physiology

Corticosteroids are synthesized in the adrenal cortex and can be divided into mineralocorticoids and glucocorticoids. The main mineralocorticoid is aldosterone and the main glucocorticoid cortisol. In addition, the adrenal secretes a large amount of androgens through dehydroepiandrosterone (DHEA) and its sulphated derivative DHEAS. Aldosterone binds to mineralocorticoid receptors (MRs) and is important in sodium handling in the kidney and other mineralocorticoid target tissues. Although the supply of the initial precursors for aldosterone production is regulated by pituitary adrenocorticotropic hormone (ACTH), a more important regulator is the renin–angiotensin system. Aldosterone production is thus maintained in adrenal insufficiency induced by pituitary disease but is lost at an early stage in conditions that destroy the adrenal gland (eg, autoimmune Addison's disease).

Cortisol is the main glucocorticoid synthesized in humans. An area of potential confusion is that cortisol is traditionally called hydrocortisone when administered as a pharmaceutical. Cortisol can bind to the glucocorticoid receptor (GR), which is expressed at varying levels in almost all cells. This binding accounts for the majority of responses seen in healthy individuals. Cortisol also has some mineralocorticoid activity because it can bind to the MR. This binding is normally limited by the presence of an enzyme in mineralocorticoid target tissues, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which rapidly inactivates cortisol to its inactive

metabolite cortisone [6]. This enzyme does not inactivate aldosterone, leaving this steroid free to bind to the MR. When cortisol levels are moderately high, however, the mineralocorticoid action of cortisol becomes clinically significant [7]. Cortisol is rapidly synthesized in the adrenal cortex in response to ACTH synthesized in the pituitary. ACTH is secreted from the pituitary in response to corticotropin releasing hormone (CRH), which is secreted from the hypothalamus. CRH is released in response to a range of factors, including neurological inputs entraining the normal diurnal rhythm of cortisol secretion and a range of physiological and psychological stressors.

DHEA is a weak adrenal androgen of uncertain physiological importance. Most of the DHEA in the circulation exists as DHEAS. DHEA is thought to exert its actions primarily through downstream conversion to more powerful androgens, such as androstenedione and testosterone in various tissues [8]. DHEA synthesis is ACTH dependent, but there may also be mechanisms within the adrenal gland that can control the relative production of glucocorticoids and adrenal androgens [9].

Steroid hormones bind to circulating binding proteins. Circulating cortisol is heavily bound to a specific binding protein, cortisol binding globulin (CBG; also known as transcortin), and to a lesser extent to albumin [10,11]. In healthy individuals, as little as 5% of cortisol will be present as a free fraction in the circulation, but only this fraction can diffuse into the tissues. Because the levels of CBG are very low at a tissue level under normal circumstances, the tissue cortisol level will actually be much lower than suggested by measurements of serum concentrations (0.1-1 μg/dL [1-20 nmol/L] compared with 7-14 μg/dL [200-400 nmol/L]). Congenital or acquired alteration in binding protein levels or affinity for cortisol will profoundly affect serum levels of cortisol but not the tissue level of steroid [12]. The most important situations in which CBG levels are elevated are pregnancy and during use of estrogen-based oral contraceptives. CBG levels are low in patients with severe illness, as described below. Current methods to directly measure free cortisol are technically difficult to perform and are not standardized for clinical use, although recent reports suggest that free cortisol estimation using CBG and albumin concentrations can give a reasonable approximation [13].

Whereas there has been great interest in the synthesis and secretion of corticosteroids, there has been much less interest in their metabolism. Variation in metabolism of cortisol is, however, likely to be of clinical significance both at a systemic and a tissue level.

In normal physiology, the metabolism of cortisol is dominated by the liver and the kidney [14]. A proportion of the cortisol present in serum is converted to cortisone within the kidney because of the presence of large amounts of the 11β-HSD2 enzyme within this organ. Cortisone is biologically inactive but can be converted back to cortisol in tissues that express the 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) enzyme (as described below). The liver is able to convert cortisone back to cortisol, but there are also a range of other enzymes in the liver that can metabolize cortisol and cortisone to less active, more polar metabolites that are then excreted in the urine. The balance between cortisol and cortisone interconversion and hepatic degradation is a major factor in determining the circulatory half-life of cortisol [15].

In recent years it has been realized that some tissues are able to generate active glucocorticoids from inert circulating precursors [15]. This occurs by the presence of the 11β-HSD1 enzyme that primarily converts inactive cortisone to active cortisol. This enzyme is expressed constitutively in liver, adipose, and bone tissue but additionally is expressed in a range of other tissues in response to inflammatory mediators [16-18]. The purpose of this inflammation-induced glucocorticoid activating capacity is unclear, but it may be important in dampening local inflammatory responses. Importantly, this is a situation where cortisol production is not regulated by the classical hypothalamic–pituitary–adrenal (HPA) axis.

Changes in HPA Axis During Critical Illness

Dramatic changes in HPA axis function occur at all levels during critical illness [2]. Some of these features appear common to all types of severe illness, whereas others may vary depending on the underlying condition. The nature and mechanisms underlying these changes probably change with disease duration, and attempts have been made to break these down into distinct acute, chronic, and recovery phases [19,20]. These anticipated changes are also modified by a range of external factors. These include disease-related pathology (eg, infection or hemorrhage) and treatment-related factors (eg, drugs). Changes in HPA function can be divided into those attributable to changes in cortisol secretion via central and adrenal influences and those attributable to changes at a tissue level (eg, cortisol binding or metabolism).

Central and Adrenal Changes

The most recognized change during critical illness is the dramatic increase in serum cortisol levels [21-33]. This occurs rapidly in virtually all types of acute illness. In the early phase of illness, this increase is primarily attributable to increased synthesis of cortisol in the adrenal cortex. Normal corticosteroid production rates in healthy subjects have been estimated to be approximately 10 to 17 mg of cortisol per day, a figure that varies considerably between individuals, is dependent on body composition and sex, and increases with age [34,35]. This increases substantially during acute stress, although the absolute change has been difficult to estimate and there may be differences in the increment depending on the type of stressor [28]. In trauma, hemorrhage, postoperative surgery, and cardiac arrest, cortisol concentrations have been reported to be 35 μg/dL, 15 to 20 μg/dL, 30 μg/dL, and 40 μg/dL, respectively [21-26], whereas in septic shock a much more variable range of mean cortisol values (13-63 μg/dL) has been reported [27-29,31-33,36]. The rapid increase in cortisol levels is primarily attributable to a rapid increase in hypothalamic CRH production, which leads to a corresponding increase in ACTH levels. To a lesser extent, non–ACTH-mediated effects have been implicated, such as direct cytokine-mediated stimulation of cortisol synthesis and augmentation of cortisol release by sympathetic nervous system stimulation [37]. Other features of this increase in serum cortisol are that the typical diurnal pattern of secretion is lost and the capacity of glucocorticoids to cause negative feedback inhibition of CRH and ACTH production is reduced [38].

Changes at a Tissue Level

After the acute phase of illness, cortisol levels decrease but still remain higher than in unstressed individuals [39]. It has been assumed that this persistent elevation is attributable to continued increased secretion, but other factors such as altered clearance of cortisol could also be important [28]. Metabolism of cortisol, for example, alters during acute illness. The systemic conversion of cortisone to cortisol (a reaction catalyzed by 11β-HSD1) appears to increase substantially [40]. The tissues mediating this conversion are unclear, but inflammation up-regulates 11β-HSD1 activity in a range of tissues including stromal cells such as fibroblasts [41]. This reflects non–ACTH-mediated cortisol generation and will increase the apparent half life of cortisol in the circulation as well as increase local levels of steroid in tissues expressing 11β-HSD1. Other factors that are likely to affect cortisol metabolism are renal and hepatic function. The liver is the main pathway through which cortisol is broken down, and any reduction in hepatic blood flow is likely to impair cortisol clearance. The kidneys also inactivate cortisol to cortisone, and thus reduced renal blood flow is likely to reduce this inactivation. These pathways may partly explain why there is a dissociation of the serum cortisol and ACTH levels during critical illness [42].

The other dramatic change in the HPA axis that occurs during acute illness is the rapid reduction in the levels of CBG leading to an alteration in the ratio of bound to free cortisol in the serum [13,39,43]. This effect occurs in the first few hours of all types of acute illness and is primarily thought to be attributable to decreased hepatic production of CBG. There may also be a component of CBG breakdown during sepsis. Neutrophil elastase can cleave CBG to inactive forms, and this may be a physiological mechanism to deliver free cortisol to sites of inflammation [44]. It is also possible that other changes in the binding of CBG to cortisol occur during sepsis [39]. The nature of these changes is unclear but could alter the amount of free cortisol available. The implication of this changed free to bound cortisol ratio is that the total cortisol measured in the serum will not appropriately reflect the change in bioavailable cortisol. The altered levels of CBG are also likely to alter pharmacokinetic properties of secreted cortisol or administered hydrocortisone and will complicate attempts to accurately measure cortisol production rates.

Effects of Disease Processes/Therapeutic Interventions

In addition to these expected changes in the HPA axis, many disease processes and therapeutic interventions affect HPA axis function (Fig 1). At a central level, mass lesions (eg, tumour or abscesses) could damage the hypothalamus, the pituitary, or the connections between the two. Other central nervous system (CNS) diseases such as subarachnoid hemorrhage or head injury could also induce hypopituitarism. Abnormal HPA axis function has been reported to be common in the acute phase of both head injury and subarachnoid hemorrhage [45,46] and may represent underlying vascular injury to the hypothalamus or pituitary. Sedatives have the

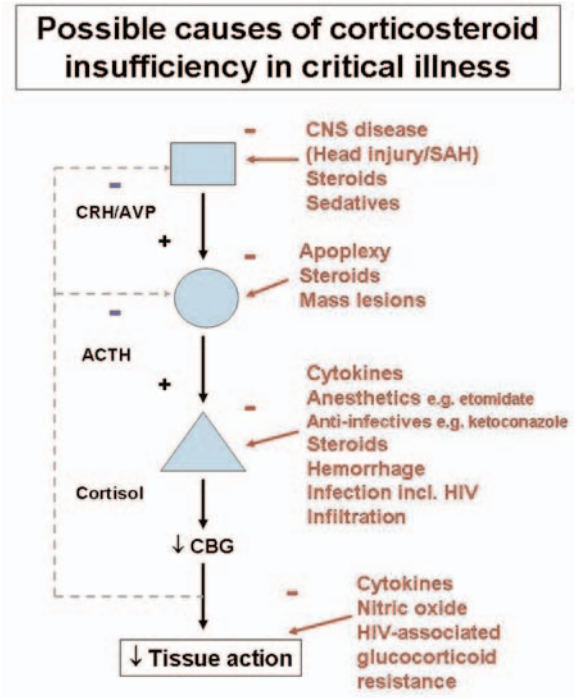

Fig 1. Possible causes of corticosteroid insufficiency in critical illness. Reduced cortisol action can arise from effects of disease or therapeutic interventions on the hypothalamus (rectangle), pituitary (circle), or adrenal (triangle) or at the tissue level. CNS = central nervous system; SAH = subarachnoid hemmorhage; CRH = corticotropin-releasing hormone; AVP = arginine vasopressin; ACTH = adrenocorticotropic hormone; CBG = cortisol binding globulin; HIV = human immunodeficiency virus.

potential to disrupt the input to the hypothalamus from other areas of the brain [47].

Many disease processes affect the adrenal glands. To induce adrenal insufficiency, the disorder would usually have to be bilateral, but adrenal hemorrhages (Waterhouse-Friderichsen syndrome [48,49]), adrenal infiltration by infections, and bilateral adrenal metastases [50] all occur relatively commonly. The adrenal cortex may also be affected at a functional level by drugs and inflammatory mediators. Inflammatory cytokines have been reported to directly stimulate cortisol release from adrenal cortical cells in some circumstances but to reduce the capacity to generate corticosteroids in response to ACTH in others [51]. Several commonly used drugs can also impair adrenal responses. The most common of these is oral corticosteroids. These are used on a chronic basis by approximately 1% of the population and almost 3% of the elderly. Because these drugs reduce endogenous ACTH secretion, a factor essential for the maintenance of adrenal cortex integrity, they can induce adrenal atrophy that may persist for weeks or months after cessation. Other drugs with a glucocorticoid-like action (eg, megestrol acetate and medroxyprogesterone) may also have this effect [52,53]. Inhaled glucocorticoids are used even more widely than oral glucocorticoids, and although they are less likely to cause adrenal atrophy, this still remains a risk [54]. Drugs used in the critical care setting such as etomidate and ketoconazole inhibit glucocorticoid synthesis, whereas others (eg, rifampicin) increase the metabolic clearance of cortisol. The impact of etomidate in a critical care setting is particularly important (recently reviewed by Jackson [55]). The introduction of this agent was associated with a dramatic increase in mortality, attributable primarily to multiorgan failure and sepsis [56]. It was subsequently determined that etomidate is a potent inhibitor of adrenal corticosteroid synthesis and when given as a continuous infusion rapidly reduced the capacity of the adrenal gland to respond to ACTH [57,58]. The use of etomidate is associated with abnormalities of ACTH stimulation test responses even after a single dose, and its use for anesthetic induction has been linked with a poor outcome in children with meningococcal septicemia [59].

Patients with HIV infection can develop adrenal failure through a range of mechanisms including infections and adrenotoxic medications, but these patients can also develop tissue glucocorticoid resistance [60].

The levels of other adrenal corticosteroids also change during critical illness. Aldosterone levels increase in response to ACTH stimulation and also with changes in the renin–angiotensin–aldosterone axis activity. The clinical importance of changes in aldosterone levels is less certain than for changes in cortisol. DHEA levels also change during critical illness. The most well documented change is the dramatic reduction in serum DHEAS levels. This has been attributed to a decrease in secretion of DHEA, a reflection of a shift away from the production of adrenal androgens to corticosteroids [61]. Although this may occur to some extent it now seems likely that DHEA production is maintained during sepsis but the generation of DHEAS from DHEA decreases [62,63]. DHEA is thought to be the biologically important hormone rather than DHEAS, so the decrease in DHEAS levels may not be biologically significant.

Corticosteroid Insufficiency

It is now well established that an absolute or relative deficiency of glucocorticoids is associated with an adverse outcome. This has been demonstrated

in patients with structural disease of the HPA axis (eg, Addison's disease [64]), patients who have previously taken high doses of glucocorticoids such that there is acquired adrenal suppression, and patients who have been exposed to drugs that block adrenal corticosteroid synthesis [56]. More controversially, it has also been hypothesized that many patients with severe illness may be unable to mount a sufficient adrenal hormone response attributable to the factors outlined above and that this would lead to an adverse outcome. If this were the case, replacement of corticosteroids would be expected to improve outlook. It is not clear, however, how frequently such insufficiency actually occurs and the level of the HPA axis affected. Although it is often implicitly assumed that the adrenal gland itself is primarily affected, there are other levels where the action of glucocorticoids could be reduced.

The clinical features of definite corticosteroid insufficiency are instructive as to what to expect in disease-related insufficiency. The best example of drug-induced corticosteroid insufficiency is the long-term use of etomidate, which, as discussed above, is now known to be a potent inhibitor of cortisol synthesis. Patients who were treated with etomidate did not exhibit clinical features suggestive of adrenal insufficiency, illustrating that clinical recognition of insufficiency in other settings is likely to be difficult.

The feature that has been most often linked with corticosteroid deficiency is hypotension that is responsive to glucocorticoid treatment [65]. Similar glucocorticoid-responsive hypotension has frequently been reported in septic shock, suggesting that adrenal gland failure may be a feature of severe sepsis. These observations suggested that failure of the adrenal gland as an organ might be a relatively common event and that replacement of glucocorticoid levels might be required routinely in this setting. This led to the concept of functional adrenal insufficiency. Implicit in this label is that there is no structural abnormality of the adrenal gland (and pathological examinations of adrenal glands of patients in this setting have not shown gross abnormalities) but corticosteroid production is impaired. This is hypothesized to be a transient effect because the majority of patients who recover have a return to normal adrenal gland function [66]. It has proven difficult to confirm whether this state actually exists and how it can be tested for biochemically [64].

In outpatient endocrine practice, a major cause of corticosteroid insufficiency is pituitary (or rarely hypothalamic) disease. In this setting, impairment of ACTH production will reduce cortisol secretion. In acute ACTH deficiency, different biochemical tests are required for diagnosis because the adrenal gland retains responsiveness to exogenous ACTH, rendering any test that depends on ACTH administration dangerously misleading. Even in patients with septic shock, secondary adrenal insufficiency appears to be a significant cause of adrenal insufficiency. Almost half of patients with adrenal insufficiency in one study had evidence of secondary adrenal insufficiency on the basis of low ACTH levels and an intact response of aldosterone to ACTH [67].

Another level where corticosteroid insufficiency could occur is within the tissue itself. Glucocorticoids need to bind to their specific receptors to have an effect, and there is evidence that variation in the number of these receptors and their affinity for glucocorticoids occurs in various settings. Manipulation of the number or sensitivity of GRs in experimental animals affects survival in response to an inflammatory challenge, with overexpression of GRs improving resistance to endotoxin-mediated septic shock [68] and receptor blockade by a GR antagonist increasing mortality [69]. Hypoxia appears to improve GR signaling in vitro [70], whereas nitric oxide has been proposed as a mediator of reduced GR function in sepsis on the basis of animal studies [71]. Inflammation has complex effects on GR number and function in humans, and peripheral blood mononuclear leukocytes isolated from patients with septic shock exhibit decreased sensitivity to glucocorticoids, a defect that recovers on disease resolution [72]. These effects are likely to vary between tissues. This raises the possibility that there may be high levels of cortisol within the tissue and available for binding to the GR but impairment of steroid binding may create a corticosteroid insufficient state within the tissue. In vivo evidence for this is weak, but if this were the case it would force a change in many of the concepts concerning adrenal insufficiency. First, it would suggest that insufficiency could occur even when the adrenal gland function was normal (thus it would not be adrenal insufficiency). Second, it would be impossible to diagnose this state on the basis of serum or even tissue levels of glucocorticoids. It would also suggest that treatment would require supraphysiological levels of glucocorticoids to achieve an adequate level of glucocorticoid action in the tissue. Other possible causes of tissue insufficiency would be alteration of glucocorticoid metabolism in the tissues (eg, failure to generate a sufficient amount of glucocorticoids locally). Again, evidence that this is a mechanism that is important in critical illness is not yet available.

Given this potential complexity, at which level is corticosteroid insufficiency likely to occur? Our view is that this will depend heavily on the underlying type of illness. In patients with septic shock, corticosteroid insufficiency will most likely be attributable to abnormalities at the adrenal or tissue level. Patients with head injuries or CNS disease will be more likely to have corticosteroid insufficiency at a central level with structurally normal adrenal glands. In other settings, defects at any of these levels might occur.

Can Adrenal Insufficiency Be Diagnosed Clinically or Biochemically?

In an outpatient setting, the symptoms and signs of adrenal insufficiency are often vague and nonspecific. As such they are easily missed. Common symptoms such as fatigue and lethargy are often only attributed to adrenal insufficiency at a late stage. More often the diagnosis of primary adrenal insufficiency is suggested by an increase in pigmentation or an abnormally raised potassium level. Adrenal insufficiency of pituitary origin is often diagnosed on the basis of symptoms attributable to other hormone deficiencies (eg, loss of libido or amenorrhea attributable to gonadotropin deficiency). It seems even more likely that signs of adrenal insufficiency will be missed or will not be apparent in the context of critical illness. Some series have suggested that eosinophilia [23,73], hyponatremia, or hypoglycemia [67] may be more common in patients with corticosteroid insufficiency, but these features are not seen consistently. Additionally, the differences between groups are not marked, and thus although they may alert the clinician in some settings, these features are not sensitive or specific enough to be used on a routine basis. Some authors have suggested that vasopressor dependency itself is a sign of corticosteroid deficiency, whereas others believe that the beneficial effects of glucocorticoids are pharmacological, attributable to reversal of vasopressor-induced adrenergic receptor desensitization [74]. It still remains unclear the extent to which glucocorticoid-induced shock reversal reflects corticosteroid insufficiency or whether this is a general feature of glucocorticoid treatment.

There is now a general consensus with regard to outpatient testing for adrenal insufficiency [75]. Although basal or random serum cortisol measurements can be helpful in some settings, their variability throughout the day and tendency to increase with mild stress reduce their diagnostic accuracy. The mainstay of testing is therefore ACTH stimulation testing. The traditional ACTH stimulation test (also referred to as the Cosyntropin, Synacthen, or tetracosactrin test) involves the baseline measurement of serum cortisol and then a subcutaneous or intravenous injection of 250 μg of synthetic ACTH(1-24). At 30 minutes after ACTH, a further serum cortisol is obtained. In this test, the basal cortisol is usually of little diagnostic importance but the absolute value of the post-ACTH cortisol is critical. If this value exceeds a defined threshold (typically 18-20 μg/dL [500-550 nmol/L], although exact values are heavily assay specific), then adrenal insufficiency is considered to be unlikely. This test is thought to reflect the capacity of the patient's adrenal cortex to respond to any future severe illness that is mimicked by the supraphysiological dose of ACTH [76]. The increment in cortisol values across this test does not give any additional information and will generally reflect either the time of day that the test is done (small increments are typically found in the morning because of the higher basal as part of the diurnal rhythm [77]) or the degree of stress that the patient is experiencing before the baseline value (with patients exposed to stressors having high basal values and thus small increments). An important feature of the test is that a baseline ACTH measurement can also be taken, and in the event of a failed test this can be used to determine whether the adrenal insufficiency has an adrenal (when ACTH would be expected to be high) or pituitary origin (when ACTH would be expected to be low or inappropriately normal). The test is useful in long-standing secondary adrenal insufficiency because deficiency in ACTH will lead to a degree of adrenal atrophy and thus a failure to acutely respond to ACTH [78]. A variation is the low-dose ACTH test. This uses 1 μg of ACTH(1-24), which leads to more physiological levels of ACTH during testing [77]. This test may be more sensitive for diagnosing mild degrees of adrenal insufficiency, but whether this is better at identifying patients who will struggle to appropriately respond to various stressors is unclear. There are some situations in which the ACTH test is not reliable. An especially important situation is in patients who have recent-onset ACTH deficiency (eg, following pituitary surgery or pituitary apoplexy). In this situation, the adrenal gland will retain responsiveness to exogenous ACTH but cortisol levels will be low because of low endogenous ACTH levels. Within 2 to 3 weeks, the lack of ACTH will lead to adrenal atrophy, and thus any ACTH testing beyond this time should become reliable again. Another limitation is the influence of

Diagnostic test	Procedure	Applicable situations	Interpretation/Caveats
Serum cortisol	Random or 0800 cortisol +/- ACTH	Highly 'stressed' patients Possible central disease	<15μg/dL (414nmol/L) suggests deficiency Depends on level of stress <15μg/dL if mild stress <25μg/dL (690nmol/L) if severe stress
Short ACTH test (250μg)	250μg ACTH(1-24) IM or IV (any time of day) 0, 30 (or 60) min cortisol	General comments	Unreliable if recent pituitary insult e.g. surgery, apoplexy.
		Peak value: Most situations except possible recent central	<20μg/dL (550nmol/L) suggests deficiency <25μg/dL may indicate hemodynamic response to glucocorticoids
		Incremental difference: Septic shock only (Not recommended in any other setting)	Increment <9μg/dL (250nmol/L) suggests beneficial response to glucocorticoids
Free cortisol index (FCI)	Random or post ACTH cortisol, CBG and albumin Free cortisol calculated	Hypoalbuminemia Sepsis Oestrogen OCP use	Reliability not proven Not standardised between centres Reference ranges not established
Free cortisol (Equilibrium dialysis)	Random or post ACTH cortisol	As for FCI	Gold standard free cortisol Little experience in critical illness Cannot be used routinely

Fig 2. Tests used to assess adrenal function during critical illness. ACTH = adrenocorticotropic hormone; IM = intramuscularly; IV = intravenously; CBG = cortisol-binding globulin; OCP = oral contraceptive pill; FCI = free cortisol index.

CBG on cortisol levels, a factor that limits the usefulness of this test in pregnancy or in individuals taking estrogen-based oral contraceptives. It also appears that there are large differences between centers in the performance of the cortisol assay, which further limits the ability to recommend uniformly applicable levels for diagnosis and treatment.

In situations where there is uncertainty or possible recent secondary insufficiency, the gold standard test is the insulin tolerance test [79]. This test involves the administration of insulin such that hypoglycemia is achieved. This test stimulates the whole of the HPA axis, and the expected response is an increase in cortisol above a threshold value (similar to that of the ACTH test). Less commonly used tests are the overnight metyrapone test, the long ACTH test, and the CRH test. Metyrapone inhibits 11β-hydroxylase, the final enzyme in corticosteroid biosynthesis. In patients with an intact HPA axis, this decrease in cortisol should lead to an increase in ACTH levels and a corresponding increase in 11-deoxycortisol levels, the precursor proximal to the 11β-hydroxylase enzyme [80]. A long ACTH test is used to distinguish between primary and secondary adrenal insufficiency because prolonged ACTH stimulation should gradually increase adrenal cortisol production in pituitary disease but not adrenal disease. These 2 tests are rarely used now because other assays that assess the axis are easier to perform and more reliable (eg, ACTH assays) and because pituitary imaging has improved.

Unfortunately, many of the assumptions underlying outpatient tests of adrenal function do not apply in critical care, and some tests are contraindicated. Most important, there is no gold standard test that can exclude adrenal insufficiency. The insulin tolerance test, for example, is not suitable for use in critically ill patients because of the risks of hypoglycemia. The types of tests that have been examined include random/basal cortisol levels (either total or free), stimulated levels following exogenous ACTH, or the increase in cortisol levels in response to ACTH (Fig 2). The potential usefulness of these tests is likely to depend on the nature of the underlying cause for adrenal insufficiency.

Any conventional test of HPA axis function assumes that the proportion of free to bound cortisol in the serum does not change. This assumption will be invalid in almost all critically ill patients because there is an increase in the free to bound ratio and a decrease in serum cortisol-binding capacity attributable to changes in CBG and albumin via the mechanisms outlined above. Attempts have been made to circumvent this issue in various ways (reviewed recently by Arafah [3]). The use of total serum cutoffs that differ in patients known to have more marked derangements in albumin (eg, those with preexisting liver disease or who develop

low albumin levels during illness) has been proposed. Alternatively, albumin and CBG can be measured in addition to serum total cortisol and equations can be used to correct the total cortisol, giving a calculated "free index." Another option is to measure free cortisol directly using equilibrium dialysis (a technique in which free but not bound cortisol can diffuse across a membrane and be measured directly) [11] or cortisol in a fluid that contains minimal binding proteins (such as saliva) [81]. These techniques are promising and have stimulated interest but are not yet proven in clinical practice. Equilibrium dialysis, for example, is a labor-intensive and relatively time-consuming technique.

Stimulation tests are the best indicators of hormonal deficiency in most endocrine systems. The use of adrenal stimulation tests in critically ill patients is complicated, however, by the fact that these patients should already have high cortisol stimulation attributable to their underlying disease. Cortisol values defined before and after ACTH in nonstressed healthy individuals may indicate adrenal insufficiency in a stressed setting. Furthermore, in normal individuals undergoing an ACTH test, cortisol levels are checked very shortly after a single dose of ACTH. If a prolonged infusion of ACTH is given, then cortisol levels continue to increase to much higher levels because of the induction of enzymes important in cortisol biosynthesis and if continued, lead to adrenal hypertrophy. If critical illness is analogous to this "long ACTH stimulation test," then the traditional cutoff values used in outpatient care for the short ACTH test would be meaningless. It would also be expected that chronically stimulated adrenal glands would be able to maintain cortisol levels with lower serum levels of ACTH, and this could account for some of the apparent dissociation between ACTH and cortisol levels, which has been suggested to be evidence of non–ACTH-mediated stimulation of cortisol synthesis. A major area of debate is whether an increment in cortisol value should occur in critically ill patients given exogenous ACTH. Some studies have suggested that an increment occurs independent of basal cortisol levels [31,82,83], whereas others have suggested that the increment decreases in proportion to baseline [5,84,85]. It is possible that these differences are attributable to the different timing of ACTH testing. Testing in the early stages of severe stress (eg, extubation [84]) would probably lead to little additional increment because the adrenal gland has not had chance to undergo any compensation. Testing of responses a few days into illness may show an increment if the adrenal glands have been able to make compensatory changes.

Another factor limiting interpretation of stimulation tests is an alteration in cortisol metabolism. An impairment in cortisol metabolism would be expected to increase cortisol levels in the serum for the same (or even lower) level of ACTH. This would invalidate the use of a universal threshold value following ACTH stimulation because this might not genuinely reflect an adequate adrenal cortisol synthetic reserve. Theoretically, the only test that would be useful in this context would be an incremental change, a high increment after ACTH regardless of the actually cortisol levels being the important measure. This use of the increment has been advocated in some settings, especially septic shock. An increase of <250 nmol/L across an ACTH test has become almost synonymous with functional adrenal insufficiency [82]. A poor increment has been linked with poor outcome in septic shock, even in people with very high basal cortisol values, and glucocorticoid supplementation in patients with a poor response might improve outcome [86,87].

Unfortunately, the use of this increment in clinical practice is fraught with difficulties. Most important, it theoretically should only have value over other tests in patients who have the most severe illness and whose HPA axis has reached equilibrium. In patients who do not have severe illness, an increment of 250 nmol/L is likely to be falsely reassuring. The best illustration of this is patients who have acute intracranial injury. Here the basal cortisol may be low because of loss of ACTH secretion, but the adrenal glands would show a brisk increment. Likewise, patients in the early stages of severe illness (eg, in the first few hours postresuscitation from prolonged cardiac arrest or immediately after extubation) would be expected to have low increments because the adrenal gland is maximally secreting cortisol [24,84]. A further problem with this test is that it appears to have poor reproducibility in septic shock when repeated in the same patients [66,88]. Patients with abnormal responses to this test on one day were no more likely to have abnormal responses to the test on the subsequent day than people who responded. This appears primarily attributable to the marked variation in serum cortisol that occurs from hour to hour, and spontaneous changes in cortisol levels that would indicate a successful pass occur commonly in these patients [89]. The use of 2 separate tests to generate the increment (rather than 1) will also negatively affect the reproducibility of the test by compounding errors estimating each of the values.

These considerations indicate that biochemical tests may be able to suggest the presence of clinically significant corticosteroid insufficiency but that

no single test would be appropriate to all situations. Clinical situations where testing schedules are likely to differ include almost all aspects of neurological critical care, treatment of patients with liver disease or marked hypoalbuminemia, and treatment of patients with septic shock.

Does Glucocorticoid Supplementation Have a Beneficial Effect?

The main reason for the study of adrenal insufficiency in critical illness is to determine whether outcome might be improved by glucocorticoid replacement or supplementation. Initial studies examining the potential benefits of steroids used high-dose regimens with broad groups of patients usually without prior testing to determine if adrenal function was satisfactory. Although these studies showed temporary improvement in surrogate markers such as vasopressor requirements, glucocorticoid use was not associated with a survival benefit in controlled trials and may have even worsened outcome. More recently, studies have examined lower doses of glucocorticoids given in prolonged courses in highly defined groups of populations, often with treatment stratified on the basis of biochemical tests. The relationship of corticosteroid supplementation to improvements in acute respiratory distress syndrome (ARDS) is also important in this setting, because this is a potential mechanism by which corticosteroids could improve outcome.

The use of very high dose steroids was stimulated by positive results in animal studies [90] and preliminary reports that suggested substantial beneficial effects in patients with septic shock [91]. These clinical studies involved a heterogeneous patient population and had methodological flaws. The issue appeared to be clarified by 3 randomized controlled trials of high-dose steroids in the mid-1980s that failed to show a significant impact of steroids on survival [92-94], conclusions supported by meta-analyses [95,96]. These studies typically used massive doses of glucocorticoids (either methylprednisolone or dexamethasone) for very short periods (24 hours or less). Although there was a suggestion that glucocorticoids caused a transient improvement in some hemodynamic parameters, any benefits were offset by later deterioration.

In the mid-1990s, there was a renewed interest in the use of lower doses of glucocorticoids intended to mimic physiological replacement (which translated to approximately 1% the steroid potency of earlier studies). These doses were also used for a much longer period of time and were generally tapered gradually. These studies suggested that the beneficial effect of glucocorticoids on shock reversal was still present at these lower doses, but a worsening of sepsis was not apparent [87,97,98]. There was a trend to a reduction in intensive treatment unit and hospital length of stay and mortality. This improvement in hemodynamics with these lower dose regimens has also been seen in several observational studies [23,86,99,100]; however, other studies have failed to show an association with improved hemodynamics or mortality [101], and others have suggested an association of a poorer outcome with corticosteroid use in a diverse critical care population [100,102,103]. Most of the studies have examined the use of glucocorticoids in patients with septic shock regardless of the results of biochemical testing and have suggested that the benefits are independent of the results. The largest study, however, divided patients into groups on the basis of the incremental response to an ACTH test, with nonresponders having increments <9 μg/dL (250 nmol/L) and responders having increments >9 μg/dL. This study was reported as showing a benefit from hydrocortisone in the nonresponders but a trend toward harm from steroids in responders. Several criticisms have been leveled at this study, including the statistical approach, the lack of power to draw conclusions about the responders, and the use of etomidate in a subset of subjects [104] (who almost universally had a poor response to ACTH on retrospective analysis). However, it remains the largest controlled trial addressing the issue of glucocorticoid replacement. Recent meta-analyses of steroid supplementation trials also suggest that low doses of corticosteroids have a beneficial effect in terms of shock reversal and mortality [105,106].

It thus still remains unclear which patients benefit from hydrocortisone supplementation and what measures should be used to define response. Although some studies have shown improved hemodynamics in a whole cohort of patients treated with steroids [107], others suggest that patients with biochemical impairment are more likely to have a response than those with normal biochemistry [23,108,109]. Although it is intuitive that improved hemodynamics would be likely to translate into improvements in morbidity and mortality, this cannot always be assumed to be the case. The other disease state that is relevant to these patients is ARDS, a condition that itself has a controversial history regarding glucocorticoid supplementation. The relationship between glucocorticoid replacement and ARDS is beyond the scope of this review, but many studies examining septic shock have overlapped with those examining ARDS. Early studies suggested that short-term high-dose steroids failed to prevent or

improve outcome in ARDS [110,111]. More recent evidence supported the use of methylprednisolone in pharmacological doses for patients with nonresolving ARDS [112], but this practice has itself been questioned because of the results of a recent large clinical trial [113]. A role for low-dose glucocorticoids in ARDS has been suggested with a subanalysis of the French multicenter trial of glucocorticoids in septic shock, where the improved outcome appeared to be primarily a result of improvement in ARDS [114]. This doubt about how glucocorticoids exert their beneficial effects inevitably makes it difficult to confidently use a particular physiological parameter as a measure of glucocorticoid deficiency or as a guide to responses to glucocorticoids in individual patients. It also makes it difficult to evaluate dose–response relationships between important variables and glucocorticoid replacement. Although doses close to physiological levels appear sufficient to provide hemodynamic support, it has been suggested that much higher levels of glucocorticoids are needed to overcome the activation of inflammatory pathways in lymphocytes [115,116]. A better understanding of these relationships would be required to confidently know whether glucocorticoid replacement should be aimed to achieve truly physiological levels, moderately supraphysiological levels (as current regimens probably do), or pharmacological levels.

Role for Measurement or Replacement of Other Adrenal Corticosteroids?

Other hormones that are lacking in complete adrenal failure are aldosterone, adrenal androgens (primarily DHEA), and adrenaline, the main hormone secreted from the adrenal medulla.

There is currently little evidence to suggest that aldosterone deficiency per se is a major problem in critically ill patients. This would be supported by clinical experience in patients with preexisting Addison's disease, where the omission of any mineralocorticoid replacement appears to be without consequence as long as cortisol/hydrocortisone levels are sufficient to replace the mineralocorticoid activity. However, fludrocortisone was used in the biggest randomized trial of corticosteroid supplementation in septic shock [87]. Adrenal androgens (DHEA) may be more important, although again they are not routinely substituted in patients with adrenal insufficiency. Clinical benefits in this setting are currently confined to quality-of-life indices [117], but a potential role in reducing cardiovascular risk is being explored. DHEA appears to have an anti-inflammatory role in some settings, and the use of DHEA supplementation during critical illness has been proposed and evaluated in animal models [32]. The use of DHEA was justified on the basis of an apparent decrease in adrenal androgen production, but recent work has cast doubt on whether adrenal androgen production actually decreases and has suggested that DHEA production is enhanced [118]. If, as seems likely, DHEA is the main active form of adrenal androgen, the rationale for using DHEA as a replacement rather than a pharmacological supplementation is weak.

Deficiency of adrenal medullary hormones is likely to occur in a range of settings, including structural disorders of the adrenal gland but also any cause of glucocorticoid deficiency because adrenal catecholamine production is dependent on high glucocorticoid concentrations from the adjacent adrenal cortex [119]. Patients who have adrenal cortical dysfunction appear to have abnormalities of cardiovascular responses [120], but the importance of this in a critical illness setting has not been explored extensively.

What Should We Do on the Basis of Current Information?

Many issues surround the practical use of glucocorticoids. Outstanding questions include which patients to test for adrenal insufficiency, which tests to use, when and how often to test, and how to interpret these tests. Should glucocorticoid treatment be based on abnormal tests or clinical factors, should all patients with specific conditions receive glucocorticoids, and should patients receive other steroids such as fludrocortisone and DHEA? If glucocorticoids are used, what are the optimal dose and duration?

The nature of the tests and their interpretation will depend on the type of underlying illness, and it may be unwise to apply criteria that work well in one setting to another. For septic shock, there is some evidence that glucocorticoid supplementation may be beneficial in patients who have a poor cortisol increment (<250 nmol/L) across an ACTH test. This test might therefore be used to select patients to treat (or not to treat) in this setting. Outside of this context, however, the assumptions underlying the use of the increment are invalid and should not be used. In patients for whom there is a clinical suspicion that adrenal dysfunction may be attributable to a problem intrinsic to the adrenal

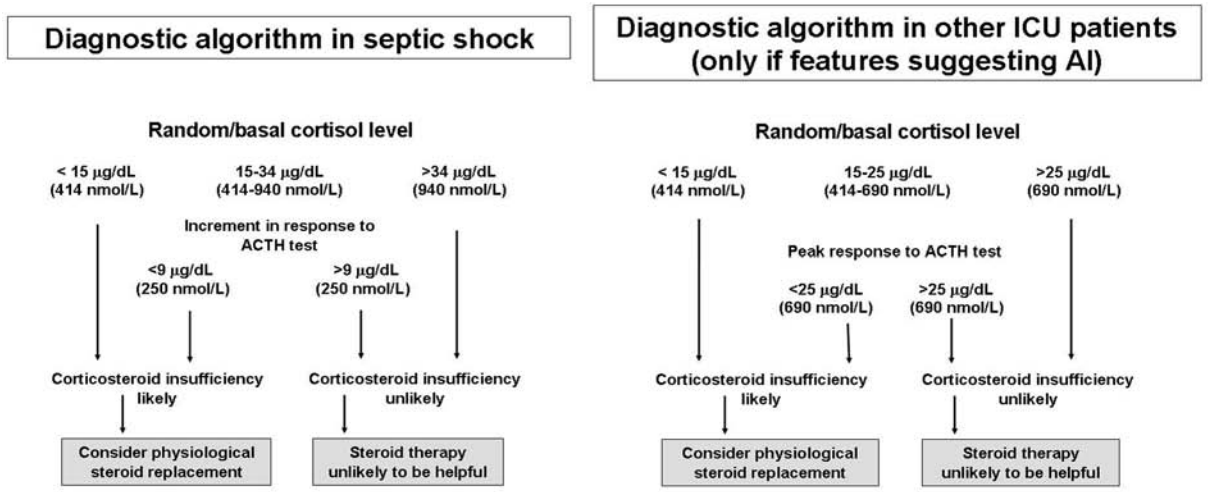

Fig 3. ACTH = adenocorticotropic hormone; ICU = intensive care unit; AI = adrenal insufficiency.

gland (or a longstanding central disease), then an ACTH stimulation test is likely to be most informative with a cutoff value applied to the cortisol value poststimulation. The best cutoff has yet to be defined, but the value of 25 μg/dL (690 nmol/L) has been recommended, and it seems reasonable to use a cutoff higher than that used in an outpatient setting because the peaks achieved during this test are on average higher than those in patients without severe illness. There are also some physiological data to support this level, with reports that septic shock patients with cortisol levels below this value are more likely to have beneficial effects on hemodynamic responses to glucocorticoid supplementation [99]. For patients in whom the critical illness is attributable to an acute intracranial event, then ACTH stimulation tests using either the increment or a post-ACTH value will be dangerously misleading. In this setting, an unstimulated cortisol will be more useful. This is likely to be influenced by the severity of the underlying illness and whether there are associated injuries, but an unstimulated value of less than 15 μg/dL (414 nmol/L) in mild stress or 25 μg/dL (690 nmol/L) in severe stress might be used to indicate patients at risk of having central adrenal insufficiency. In some settings, the underlying clinical context will be more complex and the origin of possible adrenal insufficiency unclear. In this setting, the use of an algorithm that combines a baseline cutoff with a post-ACTH stimulation test will reduce the chance of missing adrenal insufficiency from any cause (Fig 3). Low-dose ACTH testing or measurement of "free" cortisol levels should be considered research tools and should not be used to make clinical decisions. However, it would be reasonable to revise cutoff levels in patients with hypoproteinemia, and values between 10 and 15 μg/dL might be considered normal in this setting. The approach to patients with liver disease is an area where prospective data examining the effects of corticosteroid supplementation are warranted given the technical difficulty of measuring cortisol in this setting and the contrasting reports of low frequency [121] and high frequency of corticosteroid insufficiency in these patients [85,122]. Treatment of corticosteroid insufficiency should be with hydrocortisone at a dose of 50 mg every 6 to 8 hours administered as bolus injections or a continuous infusion. In patients with septic shock, this regimen will lead to cortisol levels that are higher than expected in patients who appear to make normal adrenal responses [39,107,108]. It is thus possible that lower doses may be sufficient for replacement, but until more data are available lower doses cannot be recommended. Additionally, patients without septic shock may not have such high levels of cortisol during supplementation, and the levels achieved in an individual patient would be difficult to predict. Corticosteroid supplementation should be continued until the patient's clinical situation has improved and subsequent tests have examined the HPA axis formally. In many patients, especially those who had impaired responses during septic shock, subsequent tests will be normal [29]. Tapering of the dose is usually not done before 1 week. Formal testing of the HPA axis can be performed at a later date when the patient's health has improved. There is little evidence to support the use of fludrocortisone; this might be considered in the context of septic shock to follow the regimen used in a previous clinical trial but is unlikely central to any beneficial effects.

Agenda for Future Research

There is a continuing need for research that will better define the role of corticosteroid supplementation and the prevalence and importance of corticosteroid insufficiency. A large international multicenter randomized trial of corticosteroid replacement in septic shock is ongoing and will clarify whether glucocorticoid supplementation is beneficial in this setting and whether the benefits are restricted to patients with abnormal biochemical results. Similar trials are required in other clinical settings (eg, liver disease, ARDS, haemorrhagic shock) before corticosteroid supplementation could be recommended routinely. Further work to determine markers of corticosteroids insufficiency and predictors of clinical response is also required.

The endocrinology of severe illness, particularly as it relates to intensive care, is highly topical. In terms of function of the HPA axis, abnormalities have been uncovered that if reversed or truncated might improve patient outcome. Ongoing randomized controlled trials will help to define an evidence base for therapeutic interventions in this setting.

References

1. Annane D. Glucocorticoids in the treatment of severe sepsis and septic shock. *Curr Opin Crit Care.* 2005;11:449-453.
2. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med.* 2003;348:727-734.
3. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. *J Clin Endocrinol Metab.* 2006;91:3725-3745.
4. Jacobi J. Corticosteroid replacement in critically ill patients. *Crit Care Clin.* 2006;22:245-253, vi.
5. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: a new look at an old problem. *Chest.* 2002;122:1784-1796.
6. White PC, Mune T, Agarwal.AK. 11β-Hydroxysteroid dehydrogenase and the syndrome of apparent mineralocorticoid excess. *Endocr Rev.* 1997;18:135-156.
7. Stewart PM, Walker BR, Holder G, O'Halloran D, Shackleton CH. 11β-Hydroxysteroid dehydrogenase activity in Cushing's syndrome: explaining the mineralocorticoid excess state of the ectopic adrenocorticotropin syndrome. *J Clin Endocrinol Metab.* 1995;80:3617-3620.
8. Labrie F, Luu-The V, Labrie C, et al. Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. *Endocr Rev.* 2003;24:152-182.
9. Parker LN, Levin ER, Lifrak ET. Evidence for adrenocortical adaptation to severe illness. *J Clin Endocrinol Metab.* 1985;60:947-952.
10. Rosner W. The functions of corticosteroid-binding globulin and sex hormone-binding globulin: recent advances. *Endocr Rev.* 1990;11:80-91.
11. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med.* 2004;350:1629-1638.
12. Torpy DJ, Bachmann AW, Grice JE, et al. Familial corticosteroid-binding globulin deficiency due to a novel null mutation: association with fatigue and relative hypotension. *J Clin Endocrinol Metab.* 2001;86:3692-3700.
13. Ho JT, Al Musalhi H, Chapman MJ, et al. Septic shock and sepsis: a comparison of total and free plasma cortisol levels. *J Clin Endocrinol Metab.* 2006;91:105-114.
14. Morita H, Isomura Y, Mune T, et al. Plasma cortisol and cortisone concentrations in normal subjects and patients with adrenocortical disorders. *Metabolism.* 2004;53:89-94.
15. Tomlinson JW, Walker EA, Bujalska IJ, et al. 11β-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. *Endocr Rev.* 2004;25:831-866.
16. Escher G, Galli I, Vishwanath BS, Frey BM, Frey FJ. Tumor necrosis factor-α and interleukin-1β enhance the cortisone/cortisol shuttle. *J Exp Med.* 1997;186:189-198.
17. Cooper MS, Bujalska I, Rabbitt E, et al. Modulation of 11β-hydroxysteroid dehydrogenase isozymes by proinflammatory cytokines in osteoblasts: an autocrine switch from glucocorticoid inactivation to activation. *J Bone Miner Res.* 2001;16:1037-1044.
18. Gilmour JS, Coutinho AE, Cailhier JF, et al. Local amplification of glucocorticoids by 11 beta-hydroxysteroid dehydrogenase type 1 promotes macrophage phagocytosis of apoptotic leukocytes. *J Immunol.* 2006;176:7605-7611.
19. Van den Berghe G, de Zegher F, Bouillon R. Clinical review 95: acute and prolonged critical illness as different neuroendocrine paradigms. *J Clin Endocrinol Metab.* 1998;83:1827-1834.
20. Vanhorebeek I, Van den Berghe G. The neuroendocrine response to critical illness is a dynamic process. *Crit Care Clin.* 2006; 22:1-15, v.
21. Offner PJ, Moore EE, Ciesla D. The adrenal response after severe trauma. *Am J Surg,* 2002;184:649-653.
22. Skillman JJ, Lauler DP, Hickler RB, et al. Hemorrhage in normal man: effect on renin, cortisol, aldosterone, and urine composition. *Ann Surg,* 1967;166:865-885.
23. Rivers EP, Gaspari M, Saad GA, et al. Adrenal insufficiency in high-risk surgical ICU patients. *Chest,* 2001;119:889-896.
24. Pene F, Hyvernat H, Mallet V, et al. Prognostic value of relative adrenal insufficiency after out-of-hospital cardiac arrest. *Intensive Care Med,* 2005;31:627-633.
25. Rushing GD, Britt RC, Collins JN, et al. Adrenal insufficiency in hemorrhagic shock. *Am Surg.* 2006;72:552-554.
26. Hoen S, Asehnoune K, Brailly-Tabard S, et al. Cortisol response to corticotropin stimulation in trauma patients: influence of hemorrhagic shock. *Anesthesiology.* 2002;97:807-813.
27. Schroeder S, Wichers M, Klingmuller D, 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.
28. Melby JC, Spink WW. Comparative studies on adrenal cortical function and cortisol metabolism in healthy adults and in patients with shock due to infection. *J Clin Invest.* 1958; 37:1791-1798.
29. Briegel J, Schelling G, Haller M, et al. A comparison of the adrenocortical response during septic shock and after complete recovery. *Intensive Care Med.* 1996;22:894-899.
30. Yildiz O, Doganay M, Aygen B, et al. Physiological-dose steroid therapy in sepsis [ISRCTN36253388]. *Crit Care.* 2002;6:251-259.
31. Annane D, Sebille V, Troche G, et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA.* 2000;283:1038-1045.
32. 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.
33. Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME. Cortisol levels and mortality in severe sepsis. *Clin Endocrinol (Oxf).* 2004;60:29-35.
34. Esteban NV, Loughlin T, Yergey AL, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab.* 1991;72:39-45.
35. Purnell JQ, Brandon DD, Isabelle LM, Loriaux DL, Samuels MH. Association of 24-hour cortisol production rates,

cortisol-binding globulin, and plasma-free cortisol levels with body composition, leptin levels, and aging in adult men and women. *J Clin Endocrinol Metab.* 2004;89:281-287.
36. Yildiz O, Doganay M, Aygen B, et al. Physiological-dose steroid therapy in sepsis [ISRCTN36253388]. *Crit Care.* 2002; 6:251-259.
37. Bornstein SR, Chrousos GP. Clinical review 104: adrenocorticotropin (ACTH)- and non-ACTH-mediated regulation of the adrenal cortex: neural and immune inputs. *J Clin Endocrinol Metab.* 1999;84:1729-1736.
38. Perrot D, Bonneton A, Dechaud H, Motin J, Pugeat M. Hypercortisolism in septic shock is not suppressible by dexamethasone infusion. *Crit Care Med.* 1993;21:396-401.
39. Vanhorebeek I, Peeters, RP, Vander PS, et al. Cortisol response to critical illness: effect of intensive insulin therapy. *J Clin Endocrinol Metab.* 2006;91:3803-3813.
40. 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.
41. Hardy RS, Filer A, Cooper MS, et al. Differential expression, function and response to inflammatory stimuli of 11 beta-hydroxysteroid dehydrogenase type 1 in human fibroblasts: a mechanism for tissue-specific regulation of inflammation. *Arthritis Res Ther.* 2006;8:R108.
42. Loisa P, Rinne T, Kaukinen S. Adrenocortical function and multiple organ failure in severe sepsis. *Acta Anaesthesiol Scand.* 2002;46:145-151.
43. 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.
44. Hammond GL, Smith CL, Paterson NA, Sibbald WJ. A role for corticosteroid-binding globulin in delivery of cortisol to activated neutrophils. *J Clin Endocrinol Metab.* 1990;71:34-39.
45. Aimaretti G, Ambrosio MR, Di Somma C, et al. Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. *Clin Endocrinol (Oxf).* 2004;61:320-326.
46. Kreitschmann-Andermahr I, Hoff C, Saller B, et al. Prevalence of pituitary deficiency in patients after aneurysmal subarachnoid hemorrhage. *J Clin Endocrinol Metab.* 2004;89:4986-4992.
47. Arvat E, Giordano R, Grottoli S, Ghigo E. Benzodiazepines and anterior pituitary function. *J Endocrinol Invest.* 2002; 25:735-747.
48. Waterhouse R. A case of suprarenal apoplexy. *Lancet.* 1911; I:577-578.
49. Adem PV, Montgomery CP, Husain AN, et al. Staphylococcus aureus sepsis and the Waterhouse-Friderichsen syndrome in children. *N Engl J Med.* 2005;353:1245-1251.
50. Seidenwurm DJ, Elmer EB, Kaplan LM, et al. Metastases to the adrenal glands and the development of Addison's disease. *Cancer.* 1984;54:552-557.
51. Judd AM, Call GB, Barney M, et al. Possible function of IL-6 and TNF as intraadrenal factors in the regulation of adrenal steroid secretion. *Ann N Y Acad Sci.* 2000;917:628-637.
52. Subramanian S, Goker H, Kanji A, Sweeney H. Clinical adrenal insufficiency in patients receiving megestrol therapy. *Arch Intern Med.* 1997;157:1008-1011.
53. Malik KJ, Wakelin K, Dean S, Cove DH, Wood PJ. Cushing's syndrome and hypothalamic-pituitary adrenal axis suppression induced by medroxyprogesterone acetate. *Ann Clin Biochem.* 1996;33:187-189.
54. Greenfield JR, Samaras K. Suppression of HPA axis in adults taking inhaled corticosteroids. *Thorax.* 2006;61:272-273.
55. Jackson WL Jr. Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? A critical appraisal. *Chest* 2005;127:1031-1038.
56. Watt I, Ledingham IM. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. *Anaesthesia.* 1984;39:973-981.
57. Allolio B, Stuttmann R, Fischer H, Leonhard W, Winkelmann W. Long-term etomidate and adrenocortical suppression. *Lancet.* 1983;2:626.
58. Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *N Engl J Med.* 1984;310:1415-1421.
59. den Brinker M, Joosten KF, Liem O, et al. Adrenal insufficiency in meningococcal sepsis: bioavailable cortisol levels and impact of interleukin-6 levels and intubation with etomidate on adrenal function and mortality. *J Clin Endocrinol Metab.* 2005;90:5110-5117.
60. Norbiato G, Galli M, Righini V, Moroni M. The syndrome of acquired glucocorticoid resistance in HIV infection. *Baillieres Clin Endocrinol Metab.* 1994;8:777-787.
61. Luppa P, Munker R, Nagel D, Weber M, Engelhardt D. Serum androgens in intensive-care patients: correlations with clinical findings. *Clin Endocrinol (Oxf).* 1991;34:305-310.
62. Marx C, Petros S, Bornstein SR, 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.
63. Arlt W, Hammer F, Sanning P, et al. Dissociation of serum dehydroepiandrosterone and dehydroepiandrosterone sulfate in septic shock. *J Clin Endocrinol Metab.* 2006;91:548-2554.
64. Burchard K. A review of the adrenal cortex and severe inflammation: quest of the "eucorticoid" state. *J Trauma.* 2001;51:800-814.
65. Nieboer P, van der Werf TS, Beentjes JA, et al. Catecholamine dependency in a polytrauma patient: relative adrenal insufficiency? *Intensive Care Med.* 2000;26:125-127.
66. Bouachour G, Roy PM, Guiraud MP. The repetitive short corticotropin stimulation test in patients with septic shock. *Ann Intern Med.* 1995;123:962-963.
67. Manglik S, Flores E, Lubarsky L, et al. Glucocorticoid insufficiency in patients who present to the hospital with severe sepsis: a prospective clinical trial. *Crit Care Med.* 2003;31: 1668-1675.
68. Reichardt HM, Umland T, Bauer A, Kretz O, Schutz G. Mice with an increased glucocorticoid receptor gene dosage show enhanced resistance to stress and endotoxic shock. *Mol Cell Biol.* 2000;20:9009-9017.
69. Lazar G Jr, Lazar G, Agarwal MK. Modification of septic shock in mice by the antiglucocorticoid RU 38486. *Circ Shock.* 1992;36:180-184.
70. Leonard MO, Godson C, Brady HR, Taylor CT. Potentiation of glucocorticoid activity in hypoxia through induction of the glucocorticoid receptor. *J Immunol.* 2005; 174:2250-2257.
71. Duma D, Silva-Santos JE, Assreuy J. Inhibition of glucocorticoid receptor binding by nitric oxide in endotoxemic rats. *Crit Care Med.* 2004;32:2304-2310.
72. Molijn GJ, Spek JJ, van Uffelen JC, et al. Differential adaptation of glucocorticoid sensitivity of peripheral blood mononuclear leukocytes in patients with sepsis or septic shock. *J Clin Endocrinol Metab.* 1995;80:1799-1803.
73. Beishuizen A, Vermes I, Hylkema BS, Haanen C. Relative eosinophilia and functional adrenal insufficiency in critically ill patients. *Lancet.* 1999;353:1675-1676.
74. Saito T, Fuse A, Gallagher ET, et al. The effect of methylprednisolone on myocardial beta-adrenergic receptors and cardiovascular function in shock patients. *Shock.* 1996;5: 241-246.
75. Cooper MS, Stewart PM. Diagnosis and treatment of ACTH deficiency. *Rev Endocr Metab Disord.* 2005;6:47-54.
76. 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.
77. Dickstein G, Shechner C, Nicholson WE, 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.

78. Clark PM, Neylon I, Raggatt PR, Sheppard MC, Stewart PM. Defining the normal cortisol response to the short Synacthen test: implications for the investigation of hypothalamic-pituitary disorders. *Clin Endocrinol (Oxf).* 1998;49:287-292.
79. Erturk E, Jaffe CA, Barkan AL. Evaluation of the integrity of the hypothalamic-pituitary-adrenal axis by insulin hypoglycemia test. *J Clin Endocrinol Metab.* 1998;83:2350-2354.
80. Jubiz W, Meikle AW, West CD, Tyler FH. Single-dose metyrapone test. *Arch Intern Med.* 1970;125:472-474.
81. Cohen J, Venkatesh B, Galligan J, Thomas P. Salivary cortisol concentration in the intensive care population: correlation with plasma cortisol values. *Anaesth Intensive Care.* 2004; 32:843-845.
82. Rothwell PM, Udwadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. *Lancet.* 1991;337:582-583.
83. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* 2002;288:862-871.
84. Widmer IE, Puder JJ, Konig, C, et al. Cortisol response in relation to the severity of stress and illness. *J Clin Endocrinol Metab.* 2005;90:4579-4586.
85. Tsai MH, Peng YS, Chen YC, et al. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology.* 2006;43:673-681.
86. Siraux V, De Backer D, Yalavatti G, et al. Relative adrenal insufficiency in patients with septic shock: comparison of low-dose and conventional corticotropin tests. *Crit Care Med.* 2005;33:2479-2486.
87. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* 2002;288:862-871.
88. Loisa P, Uusaro A, Ruokonen E. A single adrenocorticotropic hormone stimulation test does not reveal adrenal insufficiency in septic shock. *Anesth Analg.* 2005;101:1792-1798.
89. 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.
90. Schuler JJ, Erve PR, Schumer W. Glucocorticoid effect on hepatic carbohydrate metabolism in the endotoxin-shocked monkey. *Ann Surg.* 1976;183:345-354.
91. Schumer W. Steroids in the treatment of clinical septic shock. *Ann Surg.* 1976;184:333-341.
92. Sprung CL, Caralis PV, Marcial EH, et al. The effects of high-dose corticosteroids in patients with septic shock: a prospective, controlled study. *N Engl J Med.* 1984;311:1137-1143.
93. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis: the Veterans Administration Systemic Sepsis Cooperative Study Group. *N Engl J Med.* 1987;317:659-665.
94. Bone RC, Fisher CJ Jr, Clemmer TP, et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med.* 1987;317: 653-658.
95. Lefering R, Neugebauer EA. Steroid controversy in sepsis and septic shock: a meta-analysis. *Crit Care Med.* 1995;23: 1294-1303.
96. Cronin L, Cook DJ, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med.* 1995;23:1430-1439.
97. Briegel J, Forst H, Haller M, 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.
98. Bollaert PE, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med.* 1998;26:645-650.
99. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. *Crit Care Med.* 2003;31:141-145.
100. Markovitz BP, Goodman DM, Watson RS, Bertoch D, Zimmerman J. A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: what is the role of steroids? *Pediatr Crit Care Med.* 2005;6:270-274.
101. Rady MY, Johnson DJ, Patel B, Larson J, Helmers R. Cortisol levels and corticosteroid administration fail to predict mortality in critical illness: the confounding effects of organ dysfunction and sex. *Arch Surg.* 2005;140:661-668.
102. Britt RC, Devine A, Swallen KC, et al. Corticosteroid use in the intensive care unit: at what cost? *Arch Surg.* 2006;141: 145-149.
103. Rady MY, Johnson DJ, Patel B, Larson J, Helmers R. Corticosteroids influence the mortality and morbidity of acute critical illness. *Crit Care.* 2006;10:R101.
104. Noble DW. Dose effects of steroids on survival in sepsis. *Ann Intern Med.* 2004;141:891.
105. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ.* 2004;329:480.
106. Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. *Ann Intern Med.* 2004; 141:47-56.
107. Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med.* 2003;167:512-520.
108. Oppert M, Reinicke A, Graf KJ, et al. 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.
109. Soni A, Pepper GM, Wyrwinski PM, et al. Adrenal insufficiency occurring during septic shock: incidence, outcome, and relationship to peripheral cytokine levels. *Am J Med.* 1995;98:266-271.
110. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA. Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. *Chest.* 1987;92:1032-1036.
111. Bernard GR, Luce JM, Sprung CL, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N Engl J Med.* 1987;317:1565-1570.
112. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 1998;280:159-165.
113. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med.* 2006;354:1671-1684.
114. Annane D, Sebille V, Bellissant E. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. *Crit Care Med.* 2006;34:22-30.
115. Nakamori Y, Ogura H, Koh T, et al. The balance between expression of intranuclear NF-kappaB and glucocorticoid receptor in polymorphonuclear leukocytes in SIRS patients. *J Trauma.* 2005;59:308-314.
116. Meduri GU, Muthiah MP, Carratu P, Eltorky M, Chrousos GP. Nuclear factor-kappaB- and glucocorticoid receptor alpha- mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome: evidence for inflammation-induced target tissue resistance to glucocorticoids. *Neuroimmunomodulation.* 2005;12:321-338.
117. Arlt W, Callies F, van Vlijmen JC, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med.* 1999;341:1013-1020.
118. Kim MS, Shigenaga J, Moser A, Grunfeld C, Feingold KR. Suppression of DHEA sulfotransferase (Sult2A1) during the acute-phase response. *Am J Physiol Endocrinol Metab.* 2004;287:E731-E738.
119. Zuckerman-Levin N, Tiosano D, Eisenhofer G, Bornstein S, Hochberg Z. The importance of adrenocortical glucocorticoids

for adrenomedullary and physiological response to stress: a study in isolated glucocorticoid deficiency. *J Clin Endocrinol Metab*. 2001;86:5920-5924.
120. Stewart PM. Adrenal replacement therapy: time for an inward look to the medulla? *J Clin Endocrinol Metab*. 2004;89:3677-3678.
121. Bouachour G, Tirot P, Gouello JP, et al. Adrenocortical function during septic shock. *Intensive Care Med*. 1995;21: 57-62.
122. Marik PE, Gayowski T, Starzl TE. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med*. 2005;33:1254-1259.