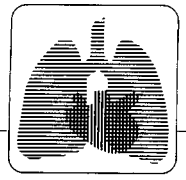

critical care review

Adrenal Insufficiency in the Critically Ill*

A New Look at an Old Problem

Paul E. Marik, MD, FCCP; and Gary P. Zaloga, MD, FCCP

Stress from many sources, including pain, fever, and hypotension, activates the hypothalamic-pituitary-adrenal (HPA) axis with the sustained secretion of corticotropin and cortisol. Increased glucocorticoid action is an essential component of the stress response, and even minor degrees of adrenal insufficiency can be fatal in the stressed host. HPA dysfunction is a common and underdiagnosed disorder in the critically ill. We review the risk factors, pathophysiology, diagnostic approach, and management of HPA dysfunction in the critically ill.

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Key words: adrenal axis; adrenal corticotropin hormone; adrenal insufficiency; cortisol; critical care; glucocorticoid receptors; hypothalamic-pituitary; ICU; sepsis; systemic inflammatory response syndrome

Abbreviations: ACTH = adrenal corticotropin hormone; CRH = corticotropin-releasing hormone; GR = glucocorticoid receptor; HD-ACTH = high-dose adrenal corticotropin stimulation; HPA = hypothalamic-pituitary-adrenal; IL = interleukin; LD-ACTH = low-dose adrenal corticotropin stimulation; Δmax = change in cortisol level following corticotropin stimulation; SIRS = systemic inflammatory response syndrome; TNF = tumor necrosis factor

Severe illness and stress activate the hypothalamic-pituitary-adrenal (HPA) axis and stimulate the release of corticotropin (also known as adrenal corticotropic hormone [ACTH]) from the pituitary, which in turn increases the release of cortisol from the adrenal cortex.[1,2] This activation is an essential component of the general adaptation to illness and stress, and contributes to the maintenance of cellular and organ homeostasis. Animals that have had adrenalectomies succumb rapidly to hemorrhagic and septic shock, and steroid replacement is protective against these challenges.[3,4] Even minor degrees of adrenal insufficiency increases the mortality of critically ill or injured patients.[5] Chronic primary adrenal insufficiency, as first described by Addison in the mid-1800s, is a rare disease.[6,7] However, acute adrenal insufficiency is a common and largely unrecognized disorder in critically ill patients. We review basic actions of glucocorticoids, etiologies for adrenal insufficiency in critically ill patients, factors affecting the release and action of cortisol, new criteria for evaluation of adrenal function during critical illness, and the treatment of adrenal insufficiency.

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Molecular Actions of Glucocorticoids

Glucocorticoids exert their effects by binding to and activating a 90-kd intracellular glucocorticoid receptor (GR) protein.[8] All cells appear to have appreciable levels of GR. The GR is localized in the cytoplasm of the cell and translocates into the nucleus on ligand binding. In the absence of hormone, cytoplasmic GR is associated with a large protein complex that includes heat shock protein-90 and heat shock protein-56.[9] This protein complex functions to maintain the GR in an inactive conformation that is competent for glucocorticoid binding. When activated by a ligand, GRs bind as dimers to glucocorticoid response elements in target genes that then activate or repress transcription of the associated genes. Hormone-activated receptors also bind as monomers to nuclear transcription factors such as nuclear factor-κB and activator protein-1.

Major Physiologic Actions of Glucocorticoids

Glucocorticoids regulate gene transcription in every cell in the body. For the purposes of this review, we highlight some of the important actions of glucocorticoids during the stress response.

Metabolic Properties

Glucocorticoids increase blood glucose levels, facilitating the delivery of glucose to cells during acute and chronic stress. Glucocorticoids increase blood glucose concentrations by increasing the rate of hepatic gluconeogenesis and inhibiting adipose tissue glucose uptake.[10] Hepatic gluconeogenesis is stimulated by increasing the activities of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase as a result of binding of glucocorticoids to the glucocorticoid response elements of the genes for these enzymes. Glucocorticoids also stimulate free fatty-acid release from adipose tissue and amino-acid release from body proteins. Major roles of these processes are to supply energy and substrate to the cell, required for the response to stress and repair from injury.

Cardiovascular System

Glucocorticoids are required for normal cardiovascular reactivity to angiotensin II, epinephrine, and norepinephrine, contributing to the maintenance of cardiac contractility, vascular tone, and BP. These effects are mediated partly by the increased transcription and expression of the receptors for these hormones.[11,12] Glucocorticoids are required for the synthesis of N+,K+-adenosine triphosphatase and catecholamines. Glucocorticoid effects on synthesis of catecholamines and catecholamine receptors are partially responsible for the positive inotropic effects of these hormones.[13] Glucocorticoids also decrease the production of nitric oxide, a major vasorelaxant and modulator of vascular permeability.[14–17]

Anti-inflammatory and Immunosuppressive Actions

Glucocorticoids possess anti-inflammatory and immunosuppressive effects that are mediated through specific receptor mechanisms.[18–21] Glucocorticoids influence most cells that participate in immune and inflammatory reactions, including lymphocytes, natural killer cells, monocytes, macrophages, eosinophils, neutrophils, mast cells, and basophils. Glucocorticoids decrease the accumulation and function of most of these cells at inflammatory sites. Most of the suppressive effects of glucocorticoids on immune and inflammatory reactions appear to be a consequence of the modulation of production or activity of cytokines (*ie*, interleukin [IL]-1, IL-2, IL-3, IL-6, interferon-γ, tumor necrosis factor [TNF]-α), chemokines, eicosanoids, complement activation, and other inflammatory mediators (*ie*, bradykinin, histamine, macrophage migration inhibitory factor). Glucocorticoids control mediator production predominantly through inhibition of transcription factors such as nuclear factor-κB.[20,21] This inhibition is mediated by induction of the IκBα inhibitory protein.[22] Glucocorticoids also produce anti-inflammatory effects by enhancing release of anti-inflammatory factors such as IL-1 receptor antagonist, soluble TNF receptor, and IL-10.[23,24] Glucocorticoids also block the transcription of messenger RNA for enzymes required for the synthesis of some mediators (*ie*, cyclooxygenase-2, inducible nitric oxide synthase).[25,26] Furthermore, by stimulating the synthesis of lipocortin-1, cortisol inhibits phospholipase A_2 (another enzyme important in the inflammatory response).

Regulation of Cortisol Secretion

Cortisol secretion by the adrenal cortex is under control of the HPA axis. Signals from the body (*ie*, cytokine release, tissue injury, pain, hypotension, hypoglycemia, hypoxemia) are sensed by the CNS and transmitted to the hypothalamus. The hypothalamus integrates these signals and increases or decreases the release of corticotropin-releasing hormone (CRH). CRH circulates to the anterior pituitary gland where it stimulates the release of ACTH, which in turn circulates to the adrenal cortex where it stimulates the release of cortisol, androgens, and aldosterone. Importantly, androgens and aldosterone release are not under primary control of ACTH. Androgens are primarily regulated by gonadotropins from the pituitary gland, and aldosterone primarily responds to the renin-angiotensin system and potassium levels. Cortisol, released from the adrenal glands or from exogenous sources, feeds back on the HPA axis to inhibit secretion (*ie*, negative feedback). Via the above-mentioned mechanisms, the body can control the secretion of cortisol within relatively narrow limits and can respond with increased secretion of cortisol to a variety of stresses and other signals.

Cortisol circulates in the blood in a bound and unbound form. The bound form is primarily carried on cortisol binding globulin (90%). It is the unbound or free cortisol that is physiologically active and homeostatically regulated. Unfortunately, current clinical assays measure total (bound and unbound) rather than free cortisol. Although free cortisol levels have not been

well studied, recent evidence suggests that in critically ill patients there is a decrease in cortisol binding with an increase in the free fraction.[27]

Cytokines and the HPA Axis

The HPA axis and the immune response are linked in a negative feedback loop in which activated immune cells produce cytokines that signal the brain. Activation of the HPA axis by specific cytokines increases the release of cortisol that in turn feeds back and suppresses the immune reaction (and further cytokine release).[28] IL-1α, IL-1β, and IL-6 administered peripherally increase HPA activity, increasing levels of CRH, ACTH, and glucocorticoids.[29,30] Cytokines also affect the pituitary and adrenal cortex directly. IL-1α, IL-1β, IL-6, and TNF-α stimulate ACTH secretion from cultured pituitary preparations and IL-1α, IL-1β, and IL-6 stimulate glucocorticoid production in cultured adrenal preparations.[29,30]

Cytokines, however, also suppress the HPA axis and GR function. Chronic IL-6 elevation may blunt ACTH release.[31] In addition, TNF-α impairs CRH-stimulated ACTH release,[32,33] and a number of clinical studies have reported inappropriately low ACTH levels in patients with severe sepsis and the systemic inflammatory response syndrome (SIRS).[32,34,35] Indeed, Schroeder and coworkers[36] reported similar circulating levels of ACTH in healthy control subjects as in patients with severe sepsis. In addition, plasma from patients with septic shock impairs synthesis of corticosteroids by adrenocortical cells.[37–39] TNF-α and corticostatin have been demonstrated to inhibit adrenal gland function.[33,40,41] Corticostatin ("defensin") is a peptide produced by immune cells.[42] Concentrations of corticostatin increase > 20-fold in animals with infection but not other forms of stress.[43] TNF-α has been shown to reduce adrenal cortisol synthesis by inhibiting the stimulatory actions of ACTH and angiotensin II on adrenal cells.[40,44,45] Proinflammatory cytokines have been shown to influence the number, expression, and function of the GR. IL-1α has been demonstrated to decrease GR translocation and transcription.[46] The half-life of cortisol has been demonstrated to be prolonged in sepsis; this may reflect a decreased number of GRs or decreased affinity of the receptor for its ligand.[39,47,48] Reduced activity of gluconeogenic enzymes during endotoxemia despite elevated circulating glucocorticoid levels provides further evidence to support impaired intracellular actions of glucocorticoids during sepsis.[49] In total, these data support the concept that mediators released in patients with sepsis may either stimulate or inhibit the synthesis and release of cortisol via actions on the HPA axis and GR. The pathophysiologic alterations that explain these different responses are unknown, as are the evolutionary advantages of inhibition of the HPA axis and GR.

Cortisol Response to Stress

Stress from many sources, including cold, fever, infection, trauma, emotional distress, burns, inflammatory agents, pain, hypotension, exercise, hemorrhage, and other challenges to homeostasis, stimulates the HPA axis, increasing secretion of cortisol. There is much controversy regarding levels of circulating cortisol that are considered to be an adequate response to stress.[50] Many textbooks and published articles state that the normal circulating cortisol response to stress is a level > 18 to 20 μg/dL. However, the choice of 18 to 20 μg/dL is based primarily on the response to exogenous high-dose ACTH stimulation (HD-ACTH) [250 μg][51] and the response to insulin-induced hypoglycemia in nonstressed noncritically ill patients. Endogenous stress may be produced by administering insulin to decrease blood glucose levels. However, the cortisol response varies with the degree of hypoglycemia (*ie*, level of endogenous stress). Importantly, severe hypoglycemia (glucose < 30 mg/dL) usually increases cortisol levels > 25 μg/dL, while moderate hypoglycemia (glucose, 40 to 60 mg/dL) produces cortisol levels > 20 μg/dL.[52]

Critical illness activates the HPA axis through different mechanisms, and the kinetics of the response differ from those found with the above-mentioned provocative tests. Pain, fever, hypovolemia, hypotension, and tissue damage all result in a sustained increase in corticotropin and cortisol secretion and a loss of the normal diurnal variation in these hormones.[53,54] During surgical procedures such as laparotomy, serum corticotropin and cortisol rise rapidly peaking in the immediate postoperative period and then decline to baseline levels over the next 72 h.[53] The magnitude of the postoperative increase in serum cortisol concentration is correlated with the extent of the surgery, with a peak between 30 μg/dL and 45 μg/dL in patients undergoing major surgery.[54–59] During severe illness, serum cortisol concentrations tend to be higher than those of patients undergoing major surgery.[53] In patients with multiple trauma, the serum cortisol level remains > 30 μg/dL for at least a week, with peak values between 40 μg/dL and 50 μg/dL.[60] Cortisol levels are increased in critically ill ICU patients, with the highest values being reported in those patients with the highest illness-severity scores and those with the highest mortality.[1,61] Rothwell and Lawler[62] measured the ICU admission cortisol level in a group

of 260 patients. In this study, the mean serum cortisol level was 27 μg/dL in survivors compared to 47 μg/dL in the nonsurvivors. The serum cortisol level was an independent predictor of outcome.[62] This data clearly demonstrates that the degree of activation of the HPA axis and serum cortisol level is related to the severity of the stressor. Animal and human studies demonstrate increasing serum levels of epinephrine and cortisol with increasing severity of stress, with hypotension and sepsis being two of the most intense stressors.[63,64] Based on these data, we believe that a random cortisol level (stress level) in severely stressed patients (*ie*, with hypotension, hypoxemia, burn, high fever, multiple trauma) should be > 25 μg/dL. Higher levels may be appropriate in patients with septic shock due to "tissue cortisol resistance."

The use of a threshold random (stress) serum cortisol of 25 μg/dL for the diagnosis of an adequate cortisol response to critical illness is supported by the literature.[65] Melby and Spink[47] reported a mean cortisol level of 63 μg/dL in 20 patients with shock (range, 30 to 160 μg/dL). Schein et al[66] reported a median cortisol concentration of 50.7 μg/dL (range, 5.6 to 400 μg/dL) in 37 patients with septic shock. Only 8% of these patients had a cortisol level < 25 μg/dL. Drucker and Shandling[67] reported a mean cortisol value of 45 μg/dL in 40 medical ICU patients. Chernow et al[68] reported a mean cortisol level of 32 μg/dL 1 h after moderate stress (*ie*, cholecystectomy) and 52 μg/dL 1 h after severe stress (*ie*, subtotal colectomy). Uncomplicated cholecystectomy increases cortisol concentrations to 27 to 34 μg/dL at 30 min after the start of surgery and 46 to 49 μg/dL at 5 h after the start of surgery.[69] Lamberts et al[53] reported mean± SD cortisol levels of 45 ± 3 μg/dL in patients with multiple trauma and 48 ± 2 μg/dL in patients with sepsis. We measured cortisol levels in 12 critically ill patients with hypotension secondary to acute GI bleeding; cortisol levels averaged 50 μg/dL, with a range of 32 to 100 μg/dL (unpublished data).

Rivers et al[70] studied the HPA axis in a group of vasopressor-dependent surgical patients. In a subgroup of patients treated with corticosteroids, the basal serum cortisol was 49 μg/dL in the steroid nonresponders and 20 μg/dL in those patients who were weaned from vasopressors within 24 h of the initiation of steroid treatment. Only one patient in the steroid responsive group had a baseline serum cortisol > 25 μg/dL, and only two nonresponders had a baseline level < 25 μg/dL. This study suggests that cortisol levels < 25 μg/dL are associated with steroid-responsive hypotension.

Clearly, there is no absolute serum cortisol level that distinguishes an adequate from an insufficient adrenal response. However, based on current evidence, we believe that a random (stress) cortisol level should be interpreted in conjunction with the severity of illness and 25 μg/dL is a useful threshold value for an appropriate response to critical illness. Furthermore, the random cortisol level should be interpreted in conjunction with the clinical response to steroid replacement therapy (see below).

Diagnosis of HPA Failure

As there are no clinically useful tests to assess the cellular actions of cortisol (*ie*, end-organ effects), the diagnosis of adrenal insufficiency is based on the measurement of serum cortisol levels; this has resulted in much confusion and misunderstanding.[35,50,67,71–79] Traditionally the "integrity" of the HPA axis has been assessed by the short corticotropin stimulation test (also known as the cosyntropin stimulation test). This test is usually performed by administering 250 μg of synthetic corticotropin IV and obtaining a serum cortisol before and 30 min and 60 min following corticotropin.[50,51] A 30- to 60-min serum cortisol level < 18 μg/dL or an increase in the cortisol concentration of < 9 μg/dL has been regarded by many as diagnostic of adrenal insufficiency.[50] However, these criteria were developed to assess adrenal reserve in patients with destructive diseases of the adrenal gland, and are based on responses in normal nonstressed, healthy control subjects.[50,51] We believe that the standard corticotropin stimulation test lacks sensitivity for the diagnosis of adrenal insufficiency.[50]

As discussed above, a threshold cortisol level of 18 μg/dL is inappropriately low in critically ill patients. "Normal" critically ill patients should elevate their cortisol level > 25 μg/dL. Furthermore, 250 μg of corticotropin is supraphysiologic (>100-fold higher than normal maximal-stress ACTH levels).[35,67,74–76] The very high levels of corticotropin obtained with 250 μg can override adrenal resistance to ACTH and result in a normal cortisol response (similar to the effect of insulin in patients with type 2 diabetes mellitus). Importantly, patients with normal responses to the HD-ACTH test (250 μg) may fail to respond normally to stress.[73,80] For example, Borst et al[81] described four patients with pituitary disease in whom standard HD-ACTH test results were normal. These patients failed to respond adequately to insulin-induced hypoglycemia. Discordant results between the HD-ACTH test and insulin-induced hypoglycemia have also been reported by others.[82]

Due to the decreased sensitivity of the HD-ACTH test for diagnosis of adrenal insufficiency, many investigators evaluated the use of stress levels of

ACTH (*ie*, 1 to 2 μg) for the diagnosis of adrenal insufficiency. A number of studies have demonstrated that a 1-μg dose (low-dose corticotropin stimulation [LD-ACTH] test) of corticotropin is more sensitive and specific for diagnosing primary and secondary adrenal insufficiency than the 250-μg dose of corticotropin.[34,83–87] We studied the adrenal response to LD-ACTH and HD-ACTH in 59 patients with septic shock; 11 patients (18%) failed to respond to LD-ACTH but responded to HD-ACTH.[80] These patients were believed to have adrenal resistance to ACTH. Using the cortisol response to hypotension as the "gold standard" for diagnosis of adrenal insufficiency (with a diagnostic threshold of 25 μg/dL), the sensitivity of the LD-ACTH test for diagnosis of adrenal insufficiency was 69%. The sensitivity of the HD-ACTH test was 42%. In a separate study of adrenal insufficiency in critically ill patients with HIV infection, the sensitivity of the LD-ACTH and HD-ACTH tests for diagnosis of adrenal insufficiency were 62% and 29%, respectively.[88] Due to the fairly mediocre sensitivities of the LD-ACTH test, we would recommend using the cortisol response to stress (with a diagnostic threshold of 25 μg/dL) as the diagnostic test of choice in stressed ICU patients. The adrenal reserve of unstressed patients is best determined by the LD-ACTH test.

The change in cortisol level following corticotropin stimulation (Δmax) is used by some clinicians to diagnose adrenal insufficiency.[67,71,75] However, the Δmax is a measure of adrenal reserve and not adrenal function. The increase in cortisol following administration of corticotropin should not be used as a criterion for the diagnosis of adrenal insufficiency. A maximally stressed patient may be secreting all the cortisol that his/her adrenal glands can synthesize. This patient may have an appropriately high serum cortisol but be unable to respond further following corticotropin injection (no reserve). For example, a critically ill patient with a basal stress cortisol level of 54 μg/dL that increases to 57 μg/dL with corticotropin does not have adrenal insufficiency. It is the absolute level that is of importance rather than the Δmax.

Most importantly, the administration of exogenous ACTH bypasses the CNS-hypothalamic-pituitary axis and tests the integrity of the adrenal glands directly. It is essential that one evaluate the entire axis since defects in the hypothalmic-pituitary components frequently cause adrenal insufficiency. Endogenous stresses such as hypotension, hypoxemia, fever, and hypoglycemia are superior stimuli for testing the integrity of the HPA axis than is ACTH testing. These endogenous stressors test the function of the entire HPA axis, and are therefore regarded as the "gold standards" for adrenal testing. ACTH testing is not required to diagnose adrenal insufficiency in severely stressed patients because the CNS-HPA axis should already be maximally activated. In such patients, a random stress cortisol level provides information on the integrity of the entire HPA axis. In patients in whom the level of stress is less intense (not hypotensive, hypoxemic, or in pain), the LD-ACTH test should be used to assess adrenal reserve.

The cortisol response to the short (60 min) corticotropin stimulation test may not adequately reflect the adrenal response to chronic stress (as seen during critical illness). When prolonged corticotropin elevation is produced in normal individuals by infusion of corticotropin, cortisol concentrations at 8 h averaged 54.6 ± 2.8 μg/dL (range, 35 to 85 μg/dL).[52] Thus, the level of and duration of corticotropin elevation affects the amount of cortisol secreted by the adrenal glands. Chronic stress results in responses that differ from acute stress. In addition, preexisting adrenal corticotropin tone (which affects adrenal mass) modulates the cortisol response to both stress and exogenous corticotropin stimulation.

One may also evaluate the pituitary-adrenal axis by administering CRH.[36] This test bypasses the hypothalamus but does require the integrity of the pituitary and adrenal glands. However, the sensitivity and specificity of the test for detecting adrenal insufficiency in critically ill patients has not been determined.

Taking all of these factors into account, we believe that a random cortisol level should be > 25 μg/dL in severely stressed ICU patients with normal adrenal function. It is not necessary to obtain cortisol levels at a specific time of the day since critically ill patients lose the diurnal variation in their cortisol levels.[54] In hypotensive patients with a random cortisol level < 25 μg/dL (*ie*, patients with adrenal insufficiency), the LD-ACTH and HD-ACTH tests can distinguish between primary adrenal failure, HPA-axis failure, and ACTH resistance.[80] Primary adrenal insufficiency is characterized by a low baseline (stress) cortisol level (< 25 μg/dL), which remains below 25 μg/dL with both low-dose and high-dose corticotropin. Patients with adrenal insufficiency due to HPA-axis failure have a baseline cortisol level < 25 μg/dL, and increase their cortisol levels > 25 μg/dL with both low-dose and high-dose corticotropin. ACTH resistance is characterized by a low baseline cortisol level that fails to increase > 25 μg/dL with low-dose corticotropin, but increases > 25 μg/dL with high-dose corticotropin.

In nonhypotensive critically ill patients, the normal cortisol response (30 to 60 min) after 1 to 2 μg corticotropin administration (LD-ACTH) should be

a level > 25 μg/dL. However, a random cortisol level of < 20 μg/dL in a nonhypotensive critically ill patient with unexplained fever, eosinophilia, or mental status changes may warrant a trial of replacement doses of corticosteroids.

Incidence of Adrenal Insufficiency

The incidence of adrenal insufficiency in critically ill patients is variable and depends on the underlying disease and severity of the illness. The reported incidence varies widely (0 to 77%) depending on the population of patients studied and the diagnostic criteria used to diagnose adrenal insufficiency.[35,47,66,67,70,74–76,80,89–91] However, the overall incidence of adrenal insufficiency in critically ill patients approximates 30%, with an incidence as high as 50 to 60% in patients with septic shock.[65] For example, using the criteria cited above, we diagnosed adrenal insufficiency in 36 of 59 patients (61%) with septic shock.[80] Only five of these patients (9%) met the "classic" criteria (cortisol < 18 μg/dL 60 min after 250 μg corticotropin) for adrenal insufficiency. Importantly, 27 of the 36 patients showed hemodynamic improvement following steroid replacement therapy. Rydvall[92] et al reported a 47% incidence of adrenal insufficiency in a general ICU population (using the stress cortisol level). Briegel et al[90] reported 13 of 20 patients (65%) with septic shock having a stress cortisol < 25 μg/dL. Sibbald et al[76] reported 20 of 26 septic patients (77%) stress cortisol levels < 25 μg/dL. Moran et al[93] reported a 49% incidence of adrenal insufficiency in patients with septic shock.

Clinical Features of Acute HPA Failure

Patients with chronic adrenal insufficiency usually present with a history of weakness, weight loss, anorexia, and lethargy, with some patients complaining of nausea, vomiting, abdominal pain, and diarrhea. Clinical signs include orthostatic hypotension and hyperpigmentation (primary adrenal insufficiency). Laboratory testing may demonstrate hyponatremia, hyperkalemia, hypoglycemia, and a normocytic anemia.[94] This presentation contrasts with the features of acute adrenal insufficiency (Table 1). Hypotension refractory to fluids and requiring vasopressors is the most common feature of acute adrenal insufficiency.[80,94] Patients usually have a hyperdynamic circulation that may compound the hyperdynamic profile of septic patients.[80] However, the systemic vascular resistance, cardiac output, and pulmonary capillary wedge pressure can be low, normal, or high.[65] The variability in hemodynamics reflects the combination of adrenal insufficiency and the underlying disease. However, acute adrenal insufficiency should always be excluded in critically ill patients requiring vasopressor support. CNS dysfunction is common, frequently a result of the underlying disease. Laboratory assessment may demonstrate eosinophilia and hypoglycemia. Hyponatremia and hyperkalemia are uncommon.

Table 1—*Symptoms and Signs Suggestive of Hypoadrenalism in Critically Ill Patients*

Specific features
Septic patients with hypotension resistant to volume resuscitation
Vasopressor-dependent patients
Eosinophilia (usually mild)
Hyponatremia and hyperkalemia
Hypoglycemia (rare)
Pituitary deficiencies (gonadotropin, thyroid, diabetes insipidus)
Hyperpigmentation (rare)
Vitiligo (rare)
Nonspecific features
Weakness, fatigue
Anorexia, weight loss
Nausea, vomiting
Diarrhea
Anemia
Metabolic acidosis
Unexplained fever
Unexplained mental status changes
Hyperdynamic circulation

Causes of Acute Adrenal Insufficiency in the Critically Ill

Acute adrenal insufficiency occurs in patients who are unable to increase their production of cortisol during acute stress. This includes patients with hypothalamic and pituitary disorders (secondary adrenal insufficiency) and patients with destructive diseases of the adrenal glands (primary adrenal insufficiency) [Table 2]. Secondary adrenal insufficiency is common in patients who have been treated with exogenous corticosteroids. However, the most common cause of acute adrenal insufficiency is sepsis and the SIRS.[65,80]

Destructive Disease of the Adrenal Gland

The most common cause of chronic primary adrenal insufficiency (Addison's disease) in the past was tuberculosis. However, HIV infection and other infections in immunosuppressed patients (*ie*, tuberculosis, cytomegalovirus, fungal) are currently the most important causes of primary adrenal insufficiency. The adrenal gland is the endocrine organ

Table 2—*Causes of Adrenal Insufficiency

Reversible dysfunction of the HPA axis
Sepsis/SIRS (primary and secondary AI)
Drugs
Corticosteroids (secondary AI)
Ketoconazole (primary AI)
Etomidate (primary AI)
Megesterol acetate (secondary AI)
Rifampin (increased cortisol metabolism)
Phenytoin (increased cortisol metabolism)
Metyrapone (primary AI)
Mitotane (primary AI)
Hypothermia (primary AI)
Primary AI
Autoimmune adrenalitis
HIV infection
HIV
Drugs
Cytomegalovirus infection
Antiphospholipid syndrome
Metastatic carcinoma
Lung
Breast
Kidney
Systemic fungal infections
Histoplasmosis
Cryptococcus
Blastomycosis
Tuberculosis
Acute hemorrhage
Disseminated intravascular coagulation
Meningococcemia
Anticoagulation
Secondary AI
Pituitary or metastatic tumor
Pituitary surgery or radiation
Empty-sella syndrome
Craniopharyngioma
Sarcoidosis, histiocytosis
Postpartum pituitary necrosis
HIV infection
Head trauma

*AI = adrenal insufficiency.

most commonly involved in patients with AIDS.[95–99] Human cytomegalovirus has been demonstrated in the adrenal glands of 33 to 88% of patients who die of AIDS. Less commonly, tubercle bacilli, *Cryptococcus neoformans*, *Toxoplasma gondii*, *Histoplasma capsulatum*, lymphoma, hemorrhage, or Kaposi sarcoma may involve the adrenal gland.[98] In addition, a number of drugs used in patients with HIV infection, most notably ketoconazole, megesterol acetate, and rifampin, can impair adrenal function.[100,101] Although the adrenal gland is commonly affected by opportunistic infections and tumor infiltration in AIDS, adrenal insufficiency in the outpatient setting is uncommon.[98,102] However, these patients may be unable to increase the synthesis of cortisol during stress. Using the revised diagnostic criteria, we reported adrenal insufficiency in 13 of 28 critically ill, HIV-positive patients (46%) who had not been treated with corticosteroids.[88]

Glucocorticoid-Induced Adrenal Insufficiency

Synthetic glucocorticoids are commonly used drugs. The use of these drugs is associated with suppression of the HPA axis. The degree of suppression depends on many factors, including the glucocorticoid potency, the dose, the dosing schedule, and the duration of use. The degree of suppression, however, is generally not predictable in any individual patient.[103] The use of inhaled corticosteroids in asthmatics has also been associated with varying degrees of adrenal suppression.[83,104] Systemic glucocorticoids probably do not cause significant HPA suppression when used for < 5 days. When these drugs are used for between 5 days and 30 days, the HPA axis will recover in most patients within 14 days of stopping treatment.[105] However, when used for > 30 days, it may take up to a year for the HPA axis to recover. The recovery of the HPA axis can most reliably be assessed by measurement of a random cortisol level in a stressed patient. The degree of adrenal recovery in the unstressed patient can be determined by the response to 1 μg of corticotropin.[105] However, it is important to note that supraphysiologic doses of glucocorticoids suppress both CRH production in the hypothalamus and ACTH production in the pituitary gland. This suppression can outlast the duration of adrenal suppression.[106] Therefore, a normal cortisol response to corticotropin does not conclusively predict a normal response to stress (which involves the hypothalamic-pituitary components of the axis).[107]

Sepsis and SIRS-Induced Acute Reversible Adrenal Insufficiency

There is increasing evidence of HPA insufficiency in critically ill septic patients,[35,67,74–76] which appears to result from circulating suppressive factors released during systemic inflammation.[108] Animal studies confirm the high incidence of adrenal insufficiency during sepsis.[109] It is important to recognize these patients since this disorder has a high mortality rate if untreated.[36] As discussed above, systemic inflammatory states such as sepsis are associated with both primary and secondary adrenal insufficiency that is reversible with treatment of the inflammation. The most convincing evidence of reversible adrenal failure during sepsis comes from the study of Briegel and colleagues.[90] These authors performed a HD-ACTH test in 20 patients during septic shock and after recovery. Thirteen of the 20 patients had adrenal insufficiency as defined by a stress cortisol

level of < 25 μg/dL. Remarkably, in these 13 patients the basal and simulated cortisol levels were higher after recovery than during the episode of septic shock (Fig 1). Others have similarly observed reversible dysfunction of the HPA axis during sepsis.[110]

The diagnostic criteria, as outlined above, should be used to assess the entire HPA axis during sepsis. Using these criteria, we studied 59 patients in septic shock; 15 of these patients (25%) had primary adrenal insufficiency, 10 patients (17%) had HPA-axis failure, and 11 patients (19%) ACTH resistance.[80] Surviving septic patients had return of adrenal function and did not require long-term treatment with corticosteroids.

Adrenocorticotropin and Cortisol Resistance

Patients with systemic infections (*ie*, sepsis, HIV) may acquire adrenal insufficiency associated with resistance to ACTH. In two recent studies in critically ill patients, we found that 30% of patients with septic shock and 25% of critically ill, HIV-infected patients acquired adrenal insufficiency associated with ACTH resistance.[80,88] Stress doses of exogenous corticotropin did not increase their serum cortisol levels, but pharmacologic doses of corticotropin were able to increase the levels into the normal range.

Ali and colleagues[111] reported a 40% decline in the number of GRs in the liver of septic rats. The decline in hormone-binding activity was associated with a fall in GR messenger RNA. Decreased affinity of the GR from mononuclear leukocytes of patients with sepsis has also been reported.[112] In addition, Norbiato et al[113] reported resistance to glucocorticoids in patients with AIDS. Cortisol-resistant patients had clinical evidence of adrenal insufficiency associated with decreased affinity of GRs for glucocorticoids and decreased GR function. We and others have also found that cortisol clearance from the circulation is impaired in many critically ill patients.[39,47] Decreased clearance reflects decreased tissue uptake and metabolism of cortisol.

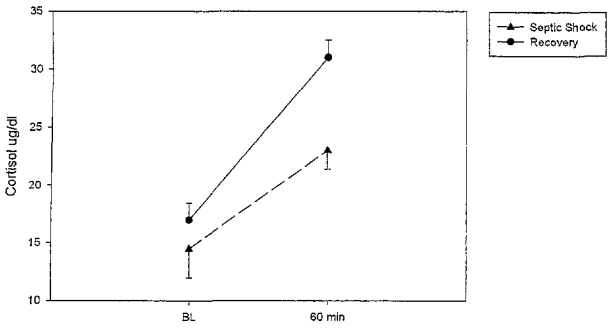

FIGURE 1. Basal and 60-min cortisol level (mean ± SD) after HD-ACTH in 13 patients with HPA insufficiency during septic shock and after recovery. Graph constructed from data extracted from study by Briegel et al.[90]

Adrenal Exhaustion Syndrome

Patients with chronic critical illness may acquire adrenal insufficiency while in the ICU. Although not evaluated in prospective trials, we have observed patients who had normal adrenal function when admitted to the ICU but later acquired adrenal insufficiency (*ie*, ARDS patient receiving long-term mechanical ventilation). The only apparent cause was a prolonged systemic inflammatory response. The adrenal insufficiency may have resulted from chronic secretion of systemic cytokines and other HPA axis-suppressive substances.[108] These patients illustrate the importance of serial follow-up of adrenal function in long-term critically ill patients.

PROGNOSIS

We believe that there is a bimodal distribution of mortality in relationship to the random cortisol level during sepsis. Patients with low cortisol levels (*ie*, < 25 μg/dL) who are not treated with corticosteroids and patients with very high levels (*ie*, > 45 μg/dL) have the highest mortality. This hypothesis may explain the apparent contradictory reports in the literature. Annane et al[71] reported a mean random cortisol level of 34 μg/dL in 189 patients with septic shock, with the nonsurvivors having higher levels than survivors (39 μg/dL vs 28 μg/dL, respectively). However, in the study of Schroeder et al[36], the mean random cortisol level was only 19 μg/dL, with nonsurvivors having a lower cortisol level than survivors (10 μg/mL vs 17 μg/dL). Most of the patients included in the study of Schroeder et al[36] would have met our criteria for adrenal insufficiency. However, none of the patients were treated with corticosteroids.

Impaired responses to corticotropin and CRH are also associated with increased mortality.[36,93] However, it remains unclear as to whether the impaired response is a direct contributor to the increased mortality or is secondary to hypothalamic-pituitary dysfunction or suppression (*ie*, from circulating mediators or elevated cortisol levels).

Treatment of Acute Adrenal Insufficiency

Deficiency of cortisol is associated with increased morbidity and mortality during critical illness. McKee and Finlay[79] randomized 18 critically ill patients with adrenal insufficiency to glucocorticoid treatment or placebo. One of 8 steroid-treated patients

(13%) died compared with 9 of 10 placebo-treated patients (90%). Evidence for high mortality from adrenal insufficiency in critically ill patients also comes from the report of Ledingham and Watt,[5] who noted increased mortality from use of etomidate (a sedative agent that causes adrenal insufficiency) in patients with multiple trauma (44% etomidate vs 27% other sedatives). The report by Ledingham and Watt emphasizes that even slight impairment of the adrenal response during severe illness can be lethal. Rivers et al[70] reported faster weaning from vasopressors and improved survival in hydrocortisone-treated patients (79% vs 55%).

Further evidence to support the benefit of glucocorticoid treatment of acute adrenal insufficiency in patients with septic shock comes from the studies of Bollaert and colleagues[114] and Briegel and coworkers.[115] Bollaert et al[114] randomized 41 patients with septic shock to hydrocortisone (100 mg IV q8h) or placebo. Although random cortisol levels were obtained, treatment with hydrocortisone was not stratified based on the levels. However, the glucocorticoid-treated patients had a significantly greater reversal of shock at 7 days and 28 days, and reduced 28-day mortality (30% vs 70%, respectively; $p = 0.09$) compared to the placebo group. Similarly, Briegel and colleagues[115] randomized 40 critically ill patients in septic shock to IV hydrocortisone or placebo. Hydrocortisone treatment was associated with improved shock reversal and decreased days of vasopressor support. There was also earlier resolution of organ dysfunction, shorter ventilator time, and shorter ICU stay. Annane et al[116] randomized 200 patients with septic shock to steroid replacement or placebo. There was a significant 30% decrease in death in the steroid-treated patients. Oppert et al[117] treated 20 patients with septic shock with hydrocortisone (10 mg/h for 7 days). Patients with "inadequate" steroid production were weaned from vasopressors significantly faster than patients with "adequate" steroid production. These studies of physiologic-stress doses of glucocorticoids administered for many days contrast with earlier studies of high-dose glucocorticoids (*ie*, 30 mg/kg of methylprednisolone) administered for one to two doses. The short-term, pharmacologic-dose studies of glucocorticoids failed to report benefit in patients with septic shock.[118,119]

Interestingly, Schelling et al[120] evaluated the effect of hydrocortisone treatment during septic shock on the incidence of posttraumatic stress disorder. The administration of hydrocortisone at stress levels during septic shock reduced the incidence of posttraumatic stress disorder and improved emotional well-being in survivors.

Perioperative Steroid Coverage

The stress of major surgery may precipitate acute adrenal insufficiency in patients with inadequate adrenal reserve (*ie*, adrenal crisis). This is especially true in patients with secondary adrenal insufficiency maintained on exogenous glucocorticoids. Prospective randomized trials have failed to adequately evaluate the dose of glucocorticoid required in various perioperative settings. Thus, recommendations for glucocorticoid coverage are based on a risk/benefit evaluation, published studies in the literature, and clinical experience. Importantly, patients undergoing major and/or prolonged operations (high level of stress) should receive stress doses of glucocorticoids before, during, and after surgery. Patients with a high likelihood of impaired gastric emptying or impaired gut absorption should receive glucocorticoid repletion via the IV route until gut function has returned to relatively normal levels. Patients should also receive sufficient steroid to control their underlying disease. Minimal doses of glucocorticoids based on type of surgery are as follows: (1) Patients undergoing minor surgery (*ie*, hernia repair, laparoscopic cholycystectomy, knee surgery) should receive a minimal dose of 25-mg hydrocortisone equivalent daily. This dose may be administered orally if gut function is intact, or IV. (2) Patients undergoing moderate surgical stress (*ie*, open cholycystectomy, partial colon resection, uncomplicated back surgery, hip replacement) should receive 50 to 75 mg/d hydrocortisone equivalent IV for 1 to 2 days. The dose may then be tapered to baseline levels based on clinical response. (3) Patients undergoing major surgical stress (*ie*, pancreatoduodenectomy, esophagectomy, total colectomy, repair for perforated bowel, cardiopulmonary bypass, ileofemoral bypass) should receive 100 to 150 mg/d hydrocortisone equivalent IV for 2 to 3 days. The dose can then be tapered to baseline doses based on clinical response. Importantly, the dose should be increased to maximal stress doses (300 mg/d hydrocortisone equivalent IV) in patients who remain hypotensive or deteriorate during recovery from surgery.[121]

Therapeutic Approach to Patients With Presumed Adrenal Insufficiency

In patients with severe stress (*ie*, hypotension, hypoxemia, pain), a random (stress) serum cortisol level should be obtained. Hypotensive patients and patients at high risk of adrenal insufficiency should be started empirically on hydrocortisone (100 mg IV q8h) pending results of testing. If the serum cortisol level returns to < 25 μg/dL, the hydrocortisone

should be continued. In addition, if the patient has improved clinically with hydrocortisone and the cortisol level is > 25 μg/dL, we favor continuing the hydrocortisone for a few days (unless there is a specific contraindication). The dose of hydrocortisone should be tapered down toward maintenance doses as the patient's clinical status improves. This treatment regimen applies to patients with primary adrenal failure, HPA-axis failure, and ACTH resistance.

In unstressed patients and in patients with a low level of physiologic stress in whom adrenal insufficiency is suspected, we favor adrenal testing with LD-ACTH (1 μg). We empirically treat the patient with hydrocortisone pending results (100 mg IV q8h). If the corticotropin stimulation test cannot be performed immediately, administer dexamethasone (2 mg) and perform the test within the next 12 h. Dexamethasone does not significantly cross-react with cortisol in the assay for cortisol and can be administered to patients pending adrenal testing.

Conclusion

HPA dysfunction is common in severely ill patients. Even slight impairment of the adrenal response to severe illness can increase morbidity and mortality, and we believe that low serum cortisol levels may be the cause, rather than the consequence, of poor outcome in these patients. Therefore, a high index of suspicion for adrenal insufficiency is required in all critically ill patients, particularly those with refractory hypotension. All patients with suspected HPA dysfunction should be treated with stress doses of corticosteroids pending the results of diagnostic testing.

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