# Mechanisms and clinical consequences of critical illness associated adrenal insufficiency

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**Purpose of review**

Adrenal insufficiency is being diagnosed with increasing frequency in critically ill patients. There exists, however, much controversy in the literature as to the nature of this entity, including its pathophysiology, epidemiology, diagnosis and treatment. The review summarizes our current understanding of the causes and consequences of adrenal insufficiency in critically ill patients.

**Relevant findings**

Activation of the hypothalamic–pituitary–adrenal axis with the production of cortisol is a fundamental component of the stress response and is essential for survival of the host. Dysfunction of the hypothalamic–pituitary–adrenal axis with decreased glucocorticoid activity is being increasingly recognized in critically ill patients, particularly those with sepsis. This condition is best referred to as 'critical illness-related corticosteroid insufficiency'. Critical illness-related corticosteroid insufficiency may occur due to dysfunction at any point in the hypothalamic–pituitary–adrenal axis including tissue glucocorticoid resistance. Critical illness-related corticosteroid insufficiency leads to an exaggerated proinflammatory response with increased tissue injury and organ dysfunction.

**Summary**

Critical illness-related corticosteroid insufficiency is common in critically ill patients, particularly those with sepsis. Supplemental corticosteroids may restore the balance between the pro-and anti-inflammatory mediators in patients with severe sepsis, septic shock and acute respiratory distress syndrome, and thereby improve the outcome of patients with these conditions.

**Keywords**

adrenal, adrenal insufficiency, cortisol, critical illness, sepsis

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**Abbreviations**

| | |
|---|---|
| **ACTH** | adrenocorticotrophic hormone |
| **ARDS** | acute respiratory distress syndrome |
| **CBG** | corticosteroid-binding globulin |
| **CIRCI** | critical illness-related corticosteroid insufficiency |
| **CRH** | corticotrophin-releasing hormone |
| **HDL** | high-density lipoprotein |
| **HPA** | hypothalamic–pituitary–adrenal |
| **SAS** | sympatho-adrenal system |
| **TNF** | tumor necrosis factor |


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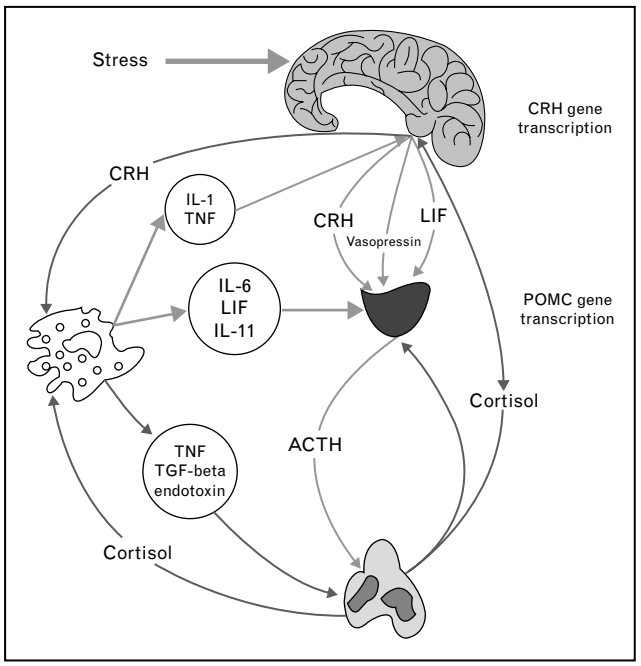
## Introduction

The stress system receives and integrates a diversity of cognitive, emotional, neurosensory and peripheral somatic signals that arrive through distinct pathways. Activation of the stress system leads to behavioral and physical changes that are remarkably consistent in their qualitative presentation. This observation was first noted by Hans Selye, who in 1936 reported that biologic, physical or psychologic stressors generally precipitate a similar response which he named the 'general adaption syndrome' or stress response [1]. The stress response is normally adaptive and time-limited, and improves the chances of the individual for survival.

The stress response is mediated largely by the hypothalamic–pituitary–adrenal (HPA) axis and the sympatho-adrenal system (SAS), which includes the sympathetic nervous system and the adrenal medulla [2–4]. Activation of the HPA and SAS systems is an essential component of the general adaptation to illness and stress, and contributes to the maintenance of cellular and organ homeostasis. The HPA axis and the SAS are functionally related. Activation of the SAS results in the secretion of epinephrine and norepinephrine from the adrenal medulla and in an increased production of inflammatory cytokines such as interleukin-6. Proinflammatory mediators such as interleukin-6 and leukemia-inhibitory factor increase transcription of the pro-opiomelanocortin gene resulting in increased production of adrenocorticotrophic hormone (ACTH) (see Fig. 1).

Activation of the HPA axis results in increased secretion from the paraventricular nucleus of the hypothalamus of corticotrophin-releasing hormone (CRH), a 41-amino acid peptide, and arginine vasopressin. CRH plays a pivotal integrative role in the response to stress. Arginine

**Figure 1 Activation of the hypothalamic–pituitary–adrenal axis (HPA) by a stressor and the interaction with the inflammatory response**




ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone; IL-6, interleukin-6; IL-11, interleukin-11; LIF, leukemia-inhibitory factor; POMC, pro-opiomelanocortin; TGF-beta, transforming growth factor-β; TNF, tumor necrosis factor.

vasopressin is a weak corticotrophin (ACTH) secretagogue, but has a synergistic role with CRH in the secretion of corticotrophin. In animal models administration of CRH will produce most of the signs associated with exposure to a stressor [5]. In addition, CRH serves as a gatekeeper of the stress response as it is subject to negative feedback on several fronts. CRH stimulates the production of ACTH by the anterior pituitary, causing the zona fasciculate of the adrenal cortex to produce more glucocorticoids (cortisol in humans). The increase in cortisol production results in multiple effects (metabolic, cardiovascular and anti-inflammatory) aiming to maintain homeostasis during stress.

## Cortisol physiology, synthesis and glucocorticoid receptors

Cortisol is the major endogenous glucocorticoid secreted by the adrenal cortex. Over 90% of circulating cortisol is bound to corticosteroid-binding globulin (CBG) with less than 10% in the free, biologically active form [6,7]. CBG is the predominant binding protein with albumin binding a lesser amount. CBG has a low capacity and high affinity, whereas albumin has a high capacity and low affinity for binding cortisol (cortisol bound to albumin is considered 'physiologically free' and active). During acute illness, particularly sepsis, CBG levels fall by as much as 50%, resulting in a significant increase in the percentage of free cortisol [8•,9]. Levels of free cortisol are also increased by elastase secreted by activated neutrophils at the site of inflammation that cleaves CBG and liberates cortisol [7]. This latter process increases the delivery of free cortisol to target cells at the site of inflammation.

The adrenal gland does not store cortisol; increased secretion arises due to increased synthesis under the control of ACTH [10]. Cholesterol is the principal precursor for steroid biosynthesis in steroidogenic tissue. In a series of sequential enzymatic steps, cholesterol is converted to pregnenolone and then to the end-products of adrenal biosynthesis, i.e. aldosterone, dehydroepiandrostenedione and cortisol [10]. The first and rate-limiting step in adrenal steroidogenesis is the formation of pregnenolone from cholesterol. At rest and during stress about 80% of circulating cortisol is derived from plasma cholesterol, the remaining 20% being synthesized *in situ* from acetate and other precursors [11]. Experimental studies suggest that high-density lipoprotein (HDL) is the preferred cholesterol source of steroidogenic substrate in the adrenal gland [12]. Recently, mouse SR-B1 (scavenger receptor, class B, type 1) and its human homolog (Cla-1) have been identified as the high-affinity HDL receptors mediating selective cholesterol uptake [13–15]. These receptors are expressed at high levels in the parenchymal cells of the liver, and the steroidogenic cells of the adrenal glands, ovary and testis [16]. Cla-1 mRNA is highly expressed in human adrenals and the accumulation of Cla-1 mRNA is regulated by ACTH in primary cultures of normal human adrenocortical cells [17].

Cortisol exerts its effects following uptake from the circulation by binding to intracellular glucocorticoid receptors [18]. These receptors belong to a steroid hormone receptor superfamily of transcription factors, which are made up of a C-terminal ligand-binding domain, a central DNA-binding domain interacting with specific DNA sequences on target genes and an N-terminal hypervariable region. The binding of cortisol to glucocorticoid receptor in the cytoplasm results in the activation of the steroid receptor complex via a process involving the dissociation of heat shock proteins (HSP90 and HSP70) as well as FK506-binding proteins [19–21].

Intracellularly, the cortisol–glucocorticoid receptor complex moves to the nucleus where it binds as a homodimer to DNA sequences called glucocorticoid-responsive elements located in the promoter regions of target genes which then activate or repress transcription of the associated genes. In addition, the cortisol–glucocorticoid receptor complex may affect cellular function indirectly by binding to and modulating the transcriptional activity of other nuclear transcription factors such as NF-κB and

activator protein-1. Overall, glucocorticoids affect the transcription of thousands of genes in every cell of the body. It has been estimated that glucocorticoids affect 20% of the genome of mononuclear blood cells [22]. In addition, the binding of corticosteroids to the glucocorticoid receptor has been demonstrated to directly non-transcriptionally increase phosphatidylinositol 3-kinase leading to activation of endothelial nitric oxide synthase [23–26].

Cortisol has several important physiologic actions on metabolism, cardiovascular function and the immune system [27,28]. The metabolic effects of cortisol include the increase in blood glucose concentrations through the activation of key enzymes involved in hepatic gluconeogenesis and inhibition of glucose uptake in adipose tissue. Additionally, in adipose tissue, lipolysis is activated resulting in the release of free fatty acids into the circulation. Cortisol also has a permissive effect on other hormones including catecholamines and glucagon, with resultant development of insulin resistance and hyperglycemia, at the expense of protein and lipid catabolism.

Glucocorticoids are required for normal cardiovascular reactivity to angiotensin II, epinephrine and norepinephrine, contributing to the maintenance of cardiac contractility, vascular tone and blood pressure. These effects are mediated partly by the increased transcription and expression of the receptors for these hormones [29,30]. Glucocorticoids are required for the synthesis of $N^+$,$K^+$-ATPase and catecholamines. Glucocorticoid effects on synthesis of catecholamines and catecholamine receptors are partially responsible for the positive inotropic effects of these hormones [31].

Glucocorticoids have potent anti-inflammatory actions including the reduction in number and function of various immune cells, such as T and B lymphocytes, monocytes, neutrophils, and eosinophils at sites of inflammation. Glucocorticoids play a major role in regulating the activity of NF-κB which plays a crucial and generalized role in inducing cytokine gene transcription [32–34]. NF-κB is normally maintained in an inactive form by sequestration in the cytoplasm through interaction with inhibitory proteins (IκBs). Upon stimulation by lipopolysaccharide, double-stranded DNA, physical and chemical stresses, and inflammatory cytokines, the latent NF-κB/IκB complex is activated by phosphorylation and proteolytic degradation of IκB, with exposure of the NF-κB nuclear localization sequence. The liberated NF-κB then translocates to the nucleus and binds to promoter regions of target genes to initiate the transcription of multiple cytokines including TNF-α, interleukin-1 and interleukin-6, and cell adhesion molecules (e.g. ICAM-1, E-selectin) and other mediators of inflammation. Glucocorticoids inhibit the activity of NF-κB by increasing the transcription of IκBs and by directly binding to and inhibiting NF-κB [33,34].

## Critical illness-related corticosteroid insufficiency

Once considered a rare diagnosis in the intensive care unit, 'adrenal insufficiency' is being reported with increased frequency in critically ill patients with sepsis, liver disease, human immunodeficiency virus infection, head injury, pancreatitis, burns and following cardiac surgery [35–40]. The reported incidence of 'adrenal insufficiency' in critically ill patients varies widely (0–77%) depending upon the population being studied and the diagnostic criteria used [35,41–51]. The incidence in medical intensive care unit patients, however, approximates 20%, being as high as 60% in patients with septic shock [28,35,43,52–54,55••]. In an elegant study recently published by Annane *et al.* [55••], the incidence of adrenal insufficiency (as determined by metyrapone testing) in patients with severe sepsis and septic shock was reported to be 60%. It is important, however, to distinguish between patients presenting to hospital with evidence of chronic adrenal insufficiency (Addison's disease) and those with 'acute adrenal insufficiency' (see Table 1). The latter is best referred to as 'critical illness-related corticosteroid insufficiency' (CIRCI). CIRCI is defined as inadequate corticosteroid activity for the severity of the patient's illness. The terms 'absolute' or 'relative' adrenal insufficiency are best avoided in the context of critical illness.

## The pathophysiology of critical illness-related corticosteroid insufficiency

The mechanisms leading to dysfunction of the HPA axis during critical illness are complex and poorly understood, and likely include decreased production of CRH, ACTH and cortisol as well as their receptors. A subset of patients may suffer structural damage to the adrenal gland from either hemorrhage or infarction and this may result in long-term adrenal dysfunction. Adrenal hemorrhage has been described with blunt abdominal trauma, following major surgery, in disseminated intravascular coagulation associated with sepsis, and in patients with burns, heparin-induced thrombocytopenia and the antiphospholipid syndrome; however, it appears that many critically ill patients develop reversible dysfunction of the HPA axis. Decreased production of cortisol and/or ACTH is particularly common in patients with severe sepsis and septic shock. Tissue resistance to cortisol may also occur due to abnormalities of the glucocorticoid receptor or increased tissue conversion of cortisol to cortisone. In addition, patients who have been treated with 'long-term' corticosteroids are likely to have secondary adrenal insufficiency which may increase the risk of developing adrenal insufficiency.

**Table 1 Causes of adrenal insufficiency**

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| Reversible dysfunction of the hypothalamic–pituitary–adrenal axis |
| Sepsis/systemic inflammatory response syndrome |
| Drugs |
| Corticosteroids (secondary adrenal insufficiency) |
| Ketoconazole (primary adrenal insufficiency) |
| Etomidate (primary adrenal insufficiency) |
| Megesterol acetate (secondary adrenal insufficiency) |
| Rifampin (increased cortisol metabolism) |
| Phenytoin (increased cortisol metabolism) |
| Metyrapone (primary adrenal insufficiency) |
| Mitotane (primary adrenal insufficiency) |
| Hypothermia (primary adrenal insufficiency) |
| Primary adrenal insufficiency |
| Autoimmune adrenalitis |
| HIV infection |
| HIV |
| Drugs |
| Cytomegalovirus infection |
| Metastatic carcinoma |
| Lung |
| Breast |
| Kidney |
| Systemic fungal infections |
| Histoplasmosis |
| Cryptococcus |
| Blastomycosis |
| Tuberculosis |
| Acute hemorrhage/infarction |
| Disseminated intravascular coagulation |
| Meningococcemia |
| Anticoagulation |
| Antiphospholipid syndrome |
| Heparin-induced thrombocytopenia |
| Trauma |
| Secondary adrenal insufficiency |
| Chronic steroid use |
| Pituitary or metastatic tumor |
| Pituitary surgery or radiation |
| Empty-sella syndrome |
| Craniopharyngioma |
| Sarcoidosis, histiocytosis |
| Postpartum pituitary necrosis |
| HIV infection |
| Head trauma |

HIV, human immunodeficiency virus.

TNF-α and interleukin-1 have been implicated in the reversible dysfunction of the HPA axis during critical illness. TNF-α impairs CRH-stimulated ACTH release, and a number of clinical studies have reported inappropriately low ACTH levels in patients with severe sepsis and the systemic inflammatory response syndrome [9,51,56–58]. In addition, septic shock has been shown to be associated with inducible nitric oxide synthase-induced neuronal apoptosis in the hypothalamus [59]. TNF-α has been shown to reduce adrenal cortisol synthesis by inhibiting the stimulatory actions of ACTH and angiotensin II on adrenal cells [60–62]. There is also evidence of decreased clearance of cortisol from the circulation likely the result of decreased cortisol uptake by cells. Proinflammatory cytokines influence the numbers, expression and function of the glucocorticoid receptor [63]. Interleukin-1 has been demonstrated to decrease glucocorticoid receptor translocation and transcription [64]. Liu *et al.* [65] demonstrated decreased expression of glucocorticoid receptors following a burn injury. It is particularly noteworthy that in the latter study the decreased expression of glucocorticoid receptors was attenuated by treatment with both anti-TNF-α and anti-interleukin-1 monoclonal antibodies. Ali *et al.* [66] reported a 40% decline in the number of glucocorticoid receptors in the liver of septic rats. The decline in hormone-binding activity was associated with a fall in glucocorticoid receptor mRNA. Decreased affinity of the glucocorticoid receptor from mononuclear leukocytes of patients with sepsis has also been reported [67]. Meduri *et al.* [68,69] have demonstrated tissue resistance to glucocorticoids with decreased nuclear translocation of the glucocorticoid receptor complex in acute respiratory distress syndrome (ARDS) patients that failed to improve or died. This phenomenon may be explained by upregulation of the dominant negative isoform glucocorticoid receptor-β and/or FKBP-52 [70,71].

Decreased production of cortisol during acute illness may also occur due to substrate deficiency. Cortisol synthesis requires increased uptake of cholesterol in the form of HDL. HDL has been shown to be substantially reduced in patients with many acute illnesses, including sepsis and burns, following myocardial infarction and in patients undergoing surgical interventions [72–80]. In patients with severe sepsis, total and HDL cholesterol levels fall rapidly, reaching 50% of the recovery levels by day 3, followed by a slow increase over the next 28 days [80]. Decreased synthesis of apoproteins has been demonstrated in hepatic cell lines exposed to TNF-α and interleukin-1β [81]. The role of substrate deficiency as a cause of adrenal insufficiency is supported by a study which demonstrated that low HDL levels in critically ill patients were associated with an attenuated response to ACTH [82]. In addition, endotoxin has been demonstrated to bind to and decrease expression of the HDL receptor (Cla-1) [83].

The major impact of corticosteroid insufficiency in the critically ill is on the systemic inflammatory response. Glucocorticoids play a central role in modulating the activation of NF-κB, the major nuclear transcription factor responsible for the production of proinflammatory mediators [19,84]. Diminished glucocorticoid activity results in excessive production of these mediators [38,84,85]. Patients with CIRCI (severe sepsis, septic shock, ARDS, etc.) are characterized by insufficient glucocorticoid activity with excessive production of proinflammatory mediators. The clinical manifestations of CIRCI are therefore those of an exaggerated inflammatory response (hypotension, fever, increased tissue injury).

## Clinical presentation

Patients with chronic adrenal insufficiency (Addison's disease) usually present with a history of weakness,

**Table 2 Symptoms and signs suggestive of critical illness-related corticosteroid insufficiency**

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| Specific features |
| Hypotension resistant to volume resuscitation |
| Eosinophilia |
| Hypoglycemia (usually mild) |
| Hyponatremia and hyperkalemia (rare and usually mild) |
| Pituitary deficiencies (gonadotrophin, thyroid, diabetes insipidus) |
| Nonspecific features |
| Unexplained fever |
| Unexplained mental status changes |
| Hyperdynamic circulation |
| Anemia |
| Metabolic acidosis |
| Nausea/vomiting |
| Diarrhea |

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. This presentation contrasts with the features of CIRCI (see Table 2). Hypotension refractory to fluids and requiring vasopressors is the most common feature of acute adrenal insufficiency [28]. CIRCI should be considered in all intensive care unit patients requiring vasopressor support. Patients usually have a hyperdynamic circulation which may compound the hyperdynamic profile of the patient with sepsis/systemic inflammatory response syndrome. The systemic vascular resistance, cardiac output and pulmonary capillary wedge pressure can, however, be low, normal or high. The variability in hemodynamics reflects the combination of CIRCI and the underlying disease. Central nervous system dysfunction is common, frequently compounded by the underlying disease. In addition, CIRCI should be considered in critically ill patients with unexplained fever. Laboratory assessment may demonstrate eosinophilia and hypoglycemia. Hyponatremia and hyperkalemia are uncommon.

## Management of critical illness-related corticosteroid insufficiency

The diagnosis of CIRCI should be considered in patients who have an exaggerated or uncontrolled proinflammatory response. This would include patients with severe sepsis, septic shock and patients with ARDS. Other patient groups such as those with burns, pancreatitis and liver failure are at an increased risk of developing CIRCI. At this time patients with CIRCI are best treated with 'moderate-dose' hydrocortisone replacement therapy (200–300 mg/day). The use of moderate-dose glucocorticoids in patients with septic shock, severe sepsis and ARDS is, however, controversial, and the risk and benefits of this therapy continue to be explored. An analysis of six randomized controlled trials which have evaluated 'moderate-dose' hydrocortisone in septic shock have demonstrated greater shock reversal (at day 7); however, the benefit in terms of mortality is less clear [52,86–89] (Sprung C, Annane D, Singer M, *et al*., in preparation). Five randomized studies have evaluated the role of treatment with glucocorticoids in patients with acute lung injury/ARDS [90–93,94•]. These studies demonstrated a 40–60% reduction in duration of mechanical ventilation with a significant reduction in mortality. Preliminary data suggest that corticosteroids may be of benefit in patients with liver failure, pancreatitis and during weaning from mechanical ventilation [95,96•,97,98•]; however, the potential benefits of treatment with hydrocortisone in these patient subgroups and other critically ill patients requires further investigation.

## Conclusion

CIRCI is a complex and frequent disorder of which our understanding continues to evolve. While CIRCI may affect a spectrum of critically ill patients most of the research has focused on patients with septic shock. At this time treatment with moderate-dose corticosteroids is recommended in patients with septic shock who have responded poorly to volume resuscitation and vasopressor agents. The consistent positive results reported in patients with acute lung injury and ARDS makes additional research in this field an urgent priority.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 456–457).


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