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Critical Illness-Related Corticosteroid Insufficiency*

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The diagnosis of adrenal failure and the indications for corticosteroid therapy in critically ill patients are controversial. This controversy is fueled by the complexity of the issues and the paucity of data from high quality clinical trials. Nevertheless, while the use of high-dose corticosteroids in patients with severe sepsis and ARDS failed to improve outcome and was associated with increased complications, an extended course of stress-dose corticosteroids has been reported to increase the occurrence of ventilator-free days and survival in select groups of ICU patients. These patients typically have an exaggerated proinflammatory response. Until recently the exaggerated proinflammatory response that characterizes critically ill patients with systemic inflammation has focused on suppression of the hypothalamic-pituitary-adrenal axis and adrenal failure. However, experimental and clinical data suggest that glucocorticoid tissue resistance may also play an important role. This complex syndrome is referred to as critical illness-related corticosteroid insufficiency (CIRCI) and is defined as inadequate corticosteroid activity for the severity of the illness of a patient. The paper reviews cortisol physiology, CIRCI, and the role of corticosteroid therapy in critically ill patients. ***(CHEST 2009; 135:181–193)***

Key words: adrenal failure; ARDS; corticosteroid insufficiency; cortisol; critical illness; glucocorticoid receptor; sepsis; septic shock; systemic inflammatory response syndrome

Abbreviations: 11β-HSD = 11β-hydroxysteroid; ACTH = adrenocorticotrophic hormone; ALI = acute lung injury; CBG = corticosteroid-binding globulin; CIRCI = critical illness-related corticosteroid insufficiency; CRH = corticotrophin releasing hormone; GC = glucocorticoid; GM-CSF = granulocyte-monocyte colony-stimulating factor; GR = glucocorticoid receptor; HDL = high-density lipoprotein; HPA = hypothalamic-pituitary-adrenal; IL-1β = interleukin-1-β; IL-6 = interleukin-6; MR = mineralocorticoid receptor; PLA2 = phospholipase A2; PTSD = post-traumatic stress disorder; RTC = randomized controlled trial; TNF-α = tumor necrosis factor-α

Exposure of the host to diverse noxious stimuli results in a stereotypic and coordinated response, referred to by Hans Selye as the "general adaption syndrome" (or stress response) which serves to restore homeostasis and enhance survival.[1] The stress response is mediated primarily by the hypothalamic-pituitary-adrenal (HPA) axis as well as the sympathoadrenal system (Fig 1).[2–4] Activation of the HPA axis results in increased secretion from the paraventricular nucleus of the hypothalamus of corticotropin-releasing hormone (CRH) and arginine vasopressin. CRH plays a pivotal integrative role in the response to stress; CRH stimulates the production of adrenocorticotrophic hormone (ACTH) by the anterior pituitary gland, causing the zona fasciculata of the adrenal cortex to produce more glucocorticoids (cortisol in humans). Arginine vasopressin is a weak ACTH secretagogue and vasoactive peptide that acts synergistically with CRH to increase secretion of ACTH. The increase in cortisol production results in multiple effects (metabolic, cardiovascular, and immune) aimed at restoring homeostasis during stress. In addition, the HPA axis and immune system are closely integrated in multiple positive

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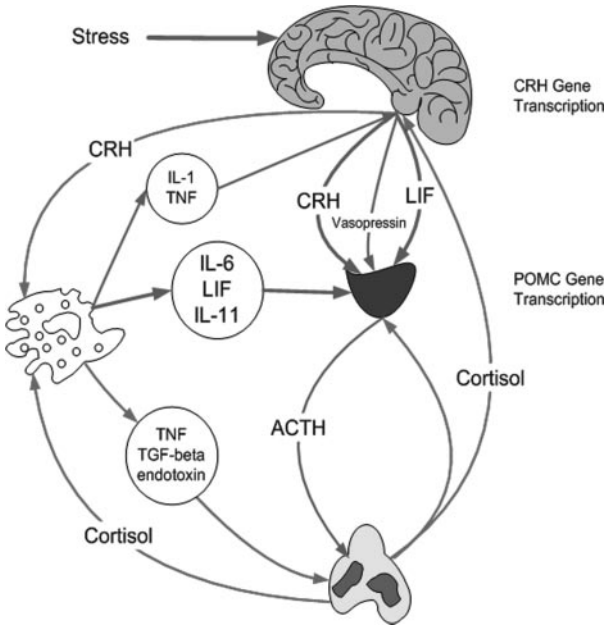

FIGURE 1. Activation of the HPA axis and the interaction with the inflammatory response. Reproduced with permission from Lippincott, Williams, and Wilkens.[34] IL-11 = interleukin-11; LIF = leukemia inhibitory factor; POMC = pro-opiomelanocortin; TGF-β = transforming growth factor-β.

and negative feed-back loops (Fig 1). Activation of the sympathoadrenal system results in the secretion of epinephrine and norepinephrine from the adrenal medulla and leads to increased production of inflammatory cytokines such as interleukin-6 (IL-6).

CORTISOL PHYSIOLOGY

Cortisol (hydrocortisone) is the major endogenous glucocorticoid secreted by the adrenal cortex. Over 90% of circulating cortisol is bound to corticosteroid-binding globulin (CBG) with $< 10\%$ in the free, biologically active form.[5,6] CBG is the predominant binding protein with albumin binding a lesser amount. During acute illness, particularly sepsis, CBG levels fall by as much as 50%, resulting in a significant increase in the percentage of free cortisol.[7,8] The circulating half-life of cortisol varies from 70 to 120 min, with a biological half-life of approximately 6 to 8 h. The adrenal gland does not store cortisol; increased secretion arises due to increased synthesis under the control of ACTH.[9] 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, namely, aldosterone, dehydroepiandrostenedione, and cortisol.[9] At rest and during stress, approximately 80% of circulating cortisol is derived from plasma cholesterol, with the remaining 20% being synthesized *in situ* from acetate and other precursors.[10] Experimental studies suggest that high-density lipoprotein (HDL) is the preferred cholesterol source of steroidogenic substrate in the adrenal gland.[11] Mouse scavenger receptor, class B, type 1 and its human homolog (Cla-1) have been identified as the high affinity HDL receptors that mediate selective cholesterol uptake.[12–14] 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.[15] Scavenger receptor, class B, type 1 knockout mice are unable to increase glucocorticoid production in response to stress or ACTH.[16]

The activity of glucocorticoids are mediated by both the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). The GR and MR share both functional and structural homology.[17] Both aldosterone and glucocorticoid hormones bind to both the GR and MR. The 11 beta-hydroxysteroid dehydrogenase (11β-HSD) enzyme plays an important role in preventing glucocorticoid access to cells that express the MR.[18,19] This enzyme has two isoforms, a NAD-dependent form (11β -HSD-2) and a NADP-dependent form (11β -HSD-1). 11β -HSD-2 is found in tissues with high levels of MR activity, such as the kidney, sweat and salivary glands, placenta, and colon. 11β -HSD-2 converts cortisol to cortisone, its inactive reduced metabolite which is unable to bind to the GR and MR. 11β -HSD-1 is found in glucocorticoid target tissues and catalyzes the conversion of cortisone to the active glucocorticoid cortisol. Pro-inflammatory cytokines modulate the activity of the 11β -HSD enzymes, with interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) increasing the activity of 11β -HSD-1, while decreasing that of 11β -HSD-2.[20,21]

Cortisol diffuses rapidly across cell membranes binding to the GR. Two isoforms of the GR have been isolated, namely GR-α and GR-β. The GR-β isoform fails to bind cortisol and activate gene expression, and thus, functions as a negative inhibitor of GR-α.[22] Recent data suggest that GR-β binds to the glucocorticoid antagonist RU-486 and may regulate gene expression.[23] Seven isoforms of GR-α have been reported; these isoforms may be selectively expressed by different tissues with each isoform eliciting a distinct response.[24,25] Through the association and disassociation of chaperone molecules the glucocorticoid-GR-α complex moves into

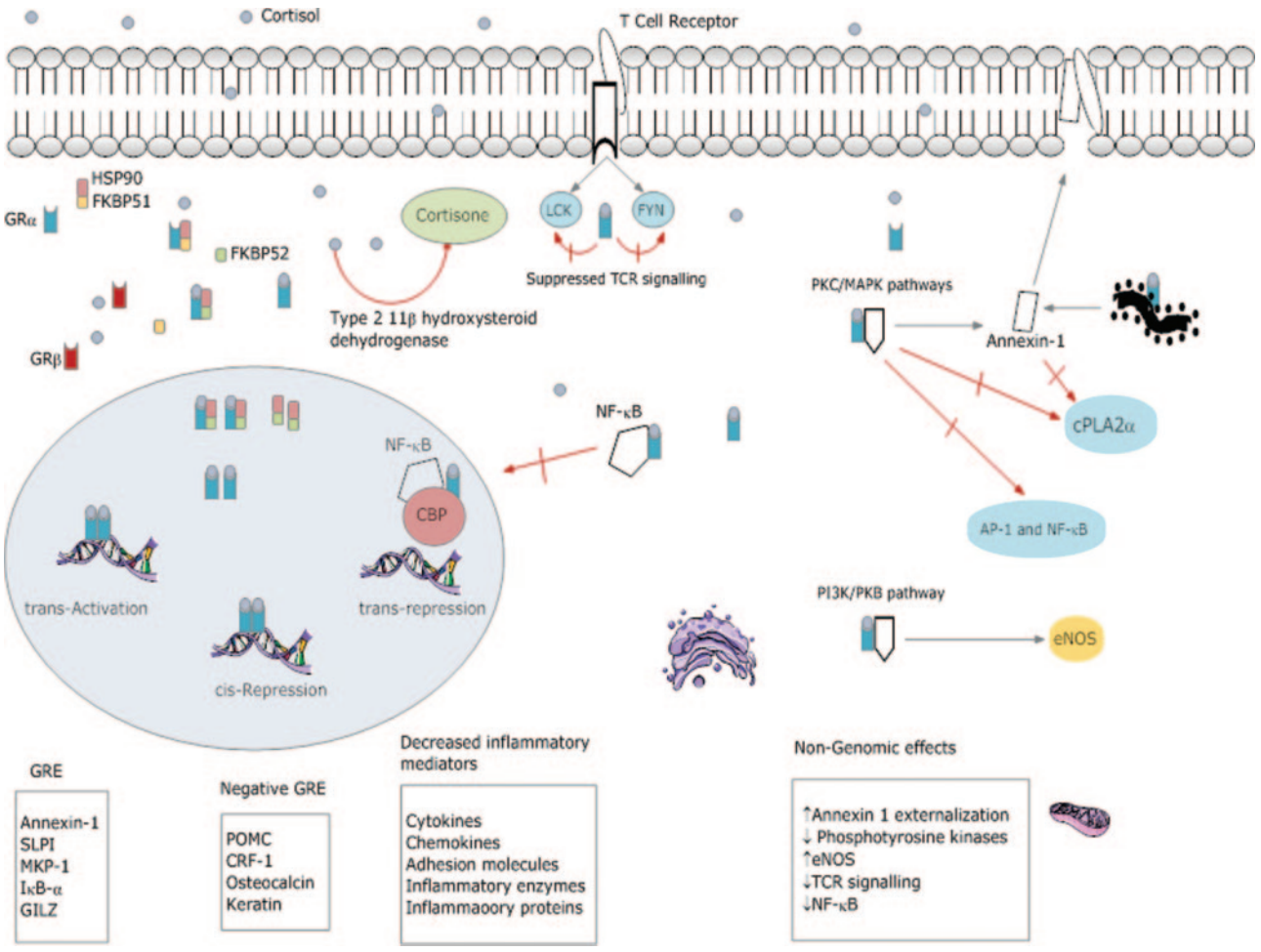

FIGURE 2. An overview of the mechanisms of action of glucocorticoids. SLP1 = secretory leukoprotease inhibitor; GILZ = glucocorticoid-induced leucine zipper protein; eNOS = endothelial nitric oxide synthetase; PI3K = phosphatidylinositol 3-kinase; PKB = protein kinase B; PKC = protein kinase C; MAPK = mitogen activated protein kinases; LCK = lymphocyte-specific protein tyrosine kinase; FYNK = FYN oncogene-related kinase; MKP-1 = MAPK phosphatase 1; HSP90 = heat shock protein 90; FKBP51/52 = FK binding protein 51/52; POMC = pro-opiomelanocortin; NF-6B = nuclear factor κ B; cPLA2α = cytosolic phospholipase A2 alpha; CBP = cyclic AMP response element binding protein.

the nucleus where it has both genomic and non-genomic (protein-protein) effects (Fig 2).[26,27]

Critical Illness-Related Corticosteroid Insufficiency

There has recently been a great deal of interest regarding the assessment of adrenal function and the indications for corticosteroid therapy in critically ill patients. While the use of high-dose corticosteroid (10,000 to 40,000 mg of hydrocortisone equivalent in > 24 h) in patients with severe sepsis and ARDS failed to improve outcome and was associated with increased complications,[28,29] an extended course of stress-dose corticosteroids (200 to 350 mg hydrocortisone equivalent per day for up to 21 days) has been demonstrated to increase ventilator- and hospital-free days, and improve short-term survival in select groups of ICU patients.[30–33] These patients typically have an exaggerated proinflammatory response and are considered to be relatively corticosteroid insufficient.

Until recently, the exaggerated proinflammatory response that characterizes patients with systemic inflammation has focused on suppression of the HPA axis and adrenal failure. However, experimental and clinical data suggest that corticosteroid tissue resistance may also play an important role. This complex syndrome is referred to as critical illness-related corticosteroid insufficiency (CIRCI).[34] CIRCI is defined as inadequate corticosteroid activity for the severity of the illness of a patient. CIRCI manifests with insufficient corticosteroid mediated downregulation of inflammatory transcription factors. Similar

to type II diabetes (relative insulin deficiency), CIRCI arises due to corticosteroid tissue resistance together with inadequate circulating levels of free cortisol.

Tissue Corticosteroid Resistance During Critical Illness

Evolutionary endocrinology provides an example of tissue corticosteroid resistance. New world monkeys (*eg*, squirrel monkey and cotton-top tamarin) over-express FK binding protein-51 (a GR chaperone), resulting in decreased nuclear translocation of the glucocorticoid-GR-α complex.[35,36] In addition, these monkeys have a transcriptionally incompetent GR.[36] To overcome this inherent corticosteroid resistance, these primates have elevated circulating levels of both free and total cortisol relative to those in old world monkeys (*eg*, humans).[35] Tissue corticosteroid resistance is a well known manifestation of chronic inflammatory diseases such as COPD, severe asthma, systematic lupus erythematosus, ulcerative colitis, and rheumatoid arthritis.[37–40] Emerging data suggest that corticosteroid tissue resistance may develop in patients with acute inflammatory diseases, such as sepsis and acute lung injury (ALI).[41]

In a sheep model of ALI induced by *Escherichia coli* endotoxin, Liu et al[42] demonstrated decreased nuclear GR-α binding capacity and increased expression of phospholipase A2 (PLA2) despite increased serum cortisol levels. These authors demonstrated similar findings in the liver cytosol following a burn injury in rats, which were partially reversed by TNF-α and IL-1β neutralizing antibodies.[43] Kino et al[44] and Kino and Chrousos[45] have demonstrated that TNF-α inhibits the transcriptional activity of the GR-α by interfering with its interaction with p160 type nuclear receptor coactivators. In an *ex vivo* model, Meduri et al[41] compared the cytoplasmic to nuclear density of the GR-complex in patients with ARDS whose conditions improved with that in patients that did not improve. These authors demonstrated a markedly reduced nuclear density of the GR-complex in patients who did not improve, while the cytoplasmic density was similar in patients who improved and in those who did not. This experiment provides further evidence that the nuclear glucocorticoid-GR activity may be impaired in critically ill patients despite adequate cytoplasmic (serum) levels of cortisol.

HPA Axis Failure in Acute Illness

HPA axis failure appears to be a common problem in patients with systemic inflammation. Patients at risk for developing tissue glucocorticoid resistance are similarly at risk for HPA axis failure. The incidence of HPA axis failure varies widely depending on the criteria used to make the diagnosis and the patient population studied. The overall incidence of adrenal insufficiency in critically ill patients is approximately 20%, with an incidence as high as 60% in patients with severe sepsis and septic shock.[46] The mechanisms leading to inadequate cortisol production during critical illness are complex, poorly understood, and likely include decreased production of CRH, ACTH, and cortisol. 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 (Table 1). In addition, a number of drugs are associated with adrenal failure. However, reversible HPA dysfunction is increasingly being recognized in critically ill patients with

Table 1—*Causes of Adrenal Insufficiency*

Reversible dysfunction of the hypothalamic-pituitary adrenal axis
Sepsis/systemic inflammatory response syndrome
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 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

systemic inflammation associated with the sepsis, ALI, liver disease, and following cardiopulmonary bypass.

TNF-α and IL-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.[47–50] TNF-α has been shown to reduce adrenal cortisol synthesis by inhibiting the stimulatory actions of ACTH and angiotensin II on adrenal cells.[51–53] Decreased production of cortisol during acute illness may occur due to substrate deficiency. 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.[54,55] van der Voort et al[56] demonstrated that in critically ill patients low HDL levels were associated with an attenuated response to cosyntropin.

Clinical Manifestations of CIRCI

Patients with chronic adrenal insufficiency (Addison Disease) 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. This presentation contrasts with the features of CIRCI. The clinical manifestations CIRCI are consequent on an exaggerated proinflammatory immune response. Hypotension refractory to fluids and requirement of vasopressors is a common manifestation of CIRCI.[57,58] CIRCI should, therefore, be considered in all ICU patients requiring vasopressor support. Patients usually have a hyperdynamic circulation that may compound the hyperdynamic profile of the patient with sepsis/systemic inflamation.[58] However, the systemic vascular resistance, cardiac output, and pulmonary capillary wedge pressure can be low, normal, or high.[59] The variability in hemodynamics reflects the combination of CIRCI and the underlying disease. CIRCI should also be considered in patients with progressive ALI. Laboratory assessment may demonstrate eosinophilia and hypoglycemia. Hyponatremia and hyperkalemia are uncommon.

Diagnosis of Adrenal Insufficiency and CIRCI

Traditionally the diagnosis of adrenal insufficiency in the critically ill has been based on the measurement of a random total serum cortisol (stress cortisol level) or the change in the serum cortisol in response to 250 ug of synthetic ACTH (cosyntropin), the so called delta cortisol.[60,61] Both of these tests have significant limitations in the critically ill.[62] Commercially available cortisol assays measure the total hormone concentration rather than the biologically active, free cortisol concentration. Furthermore, the timing of cortisol measurements may be important as large hourly variations in cortisol have been reported.[63,64] In addition, the reproducibility of the ACTH stimulation test is poor in critically ill patients.[63,64] To complicate the issue further, the specificity, sensitivity, and performance of the commercially available assays are not uniform.[65] It is speculated that the variation in assay characteristics might be even more significant in critically ill patients, especially in those with septic shock. The presence of interfering heterophile antibodies as well as cortisol precursors and metabolites may account for this observation.[66] Despite these limitations, Annane et al[46] have reported that a delta cortisol of < 9 mg/dL was the best predictor of adrenal insufficiency, as determined by metyrapone testing, in patients with severe sepsis/septic shock. A cortisol of < 10 mg/dL was also highly predictive of adrenal insufficiency (PPV of 0.93); however, the sensitivity of the test was poor (0.19). In this study, the use of calculated free cortisol did not improve the performance of the tests. It would, therefore, appear that at this time a random cortisol of < 10 mg/dL or a delta cortisol of < 9 mg/dL are the best tests for the diagnosis of adrenal insufficiency in the critically ill (high specificity, low sensitivity). As we have no test that quantifies corticosteroid activity at the tissue level, the diagnosis of CIRCI remains somewhat elusive at this time. Future studies evaluating corticosteroids in sepsis, ARDS, and other conditions manifested by systemic inflammation should measure markers of GR activity, such as GR nuclear density, annexin-1, IL-6, PLA2,and nuclear factor kappa B levels, in conjunction with tests evaluating the integrity of the HPA axis.[67]

Treatment With Corticosteroids: Who and How?

Over the last three decades, approximately 20 randomized controlled trials (RCTs) have been conducted evaluating the role of glucocorticoids in patients with sepsis, severe sepsis, septic shock, and ARDS. Varying doses (37.5 to 40,000 mg of hydrocortisone eq/day), dosing strategies (*eg*, single bolus, repeat boluses, continuous infusion, and dose taper) and duration of therapy (1 to 32 days) were used in these studies.[28,29] The results of these studies to-

gether with our current understanding of CIRCI allow us to make a number of general recommendations. It should be appreciated that the nonstressed daily production of cortisol (hydrocortisone) in adults is approximately 15 to 25 mg/day, while the maximal stressed daily production of cortisol (hydrocortisone) is approximately 200 to 350 mg/day.[68] Based on this data, a daily dose of hydrocortisone (or equivalent) of 25 to 200 mg/day can be considered low-dose, 200 to 350 mg/day a physiologic stress-dose, 351 to 1,000 mg/day as a supra-physiologic dose, and > 1,000 mg/day as high-dose corticosteroid. A number of RCTs investigated the clinical outcomes of high-dose, short course corticosteroid treatment in patients with ARDS and sepsis. Doses of methylprednisolone as high as 20 to 30 mg/kg body weight (10,000 to 40,000 mg of hydrocortisone) in > 24 h were investigated.[28,29] These studies were unable to demonstrate improved outcomes, and there was a higher incidence of complications in the patients who received high-dose corticosteroids.[28,29] This dosing strategy is at odds with our current understanding of CIRCI. Ideally, the dose of corticosteroid should be sufficient to downregulate the proinflammatory response without causing excessive immune-paresis and interfering with wound healing. Similarly, the duration of glucocorticoid therapy should be guided by the duration of CIRCI and the associated duration of systemic inflammation.

In 1991, Schneider and Voerman[69] were the first investigators to suggest that "physiologic and not pharmacologic doses of glucocorticoids [be administered] in the course of septic shock". These authors demonstrated reversal of shock in 3 of 8 patients given "100 mg of hydrocortisone IV followed by 100 mg every 8 h with dose tapering with improvement." The use of extended course, stress-dose corticosteroids has been evaluated in 10 RCTs in critically ill patients with sepsis, septic shock, and ARDS (Table 2).[30–33,70–75] Overall, this dosing strategy has been reported to be associated with a significant reduction in 28 day all-cause mortality, more rapid weaning of vasopressor agents (septic shock), a reduction in ICU length of stay, and an increase in ventilator-free days (ARDS).[28,29,34,76] While many clinicians may be reluctant to prescribe corticosteroids based on the "negative" results of the recent CORTICUS study,[75] it should be appreciated that this study has a number of serious limitations. Most notably, the lack of clinical equipoise resulted in a significant selection bias (patients least likely to benefit from corticosteroids were enrolled in the study).[77] The ARDSnet

Table 2—*Randomized Placebo-Controlled Clinical Trials Investigating the Mortality Benefit of Stress-Dose Glucocorticoids in Critically Ill Patients**

Investigated Conditions	No.	Initial Dose	Average Daily HC Equivalent, mg	Duration, d		Death, OR (95% CI)
				Rx	Taper	
General ICU patients with AI (n = 1)						
McKee and Finlay,[30] 1983	18	Hydrocortisone, 100-mg bolus then every 12 h	200	UCI	No	0.02 (0.0–0.3)
Severe sepsis/pneumonia (n = 1)						
Confalonieri et al,[31] 2005	46	Hydrocortisone, 200-mg bolus then 10 mg/h	240	7	No	0.06 (0.0–1.09)
Septic shock (n = 7)						
Bollaert et al,[70] 1998	41	Hydrocortisone, 100 mg every 8 h	300	5	6	0.27 (0.07–0.99)
Briegel et al,[71] 1999	40	Hydrocortisone, 100-mg bolus then 0.18 mg/kg/h	300	SR	6	0.71 (0.14–3.66)
Chawla et al,[72] 1999	44	Hydrocortisone, 100 mg every 8 h	300	3	4	0.39 (0.11 1.38)
Annane et al,[32] 2002	300	Hydrocortisone, 50 mg every 6 h plus fludrocortisone	200	7	No	0.76 (0.48–1.20)
Oppert et al,[73] 2005	41	Hydrocortisone, 100-mg bolus then 0.18 mg/kg/h	300	SR	4	0.69 (0.2–2.43)
Cicarelli et al,[74] 2007	29	Dexamethasone, 0.2 mg/kg every 36 h three times	190	4.5	No	0.25 (0.05–1.29)
Sprung et al,[75] 2008	499	Hydrocortisone, 50 mg every 6 h	200	5	6	1.12 (0.77–1.63)
Subtotal						0.7 (0.47–1.05)
ARDS (n = 1)						
Meduri et al,[33] 2007	91	Methylprednisolone, 1 mg/kg/d infusion	350	21†	7	0.42 (0.16–1.07)
Total						0.51 (0.31–0.83)‡

*AI = adrenal insufficiency; CI = confidence interval; Rx = treatment; SR = shock reversal; UCI = until clinical improvement.
†Up to 21 days.
‡$p = 0.007$, $I^2 = 56\%$.

Late Steroid Rescue Study investigated the role of a supra-physiologic dose of methylprednisolone (approximately 700 mg hydrocortisone equ/day) in patients with severe persistent ARDS after 7 days of ventilatory support.[78] While the design and outcome of this study has been much debated,[76,79] there was a significant increase in ventilator-free days (alive and off mechanical ventilation) in the corticosteroid group, although overall mortality was not improved. It is, however, important to recognize that both the Late Steroid Rescue Study and the study by Meduri et al[33] enrolled patients before lung protective ventilatory strategies were widely adopted. Since high tidal volume ventilation has been documented to increase the production of proinflammatory mediators,[80,81] it is possible that the benefit of corticosteroids may be limited to patients not receiving a protective ventilatory strategy. Furthermore, while the data in Table 2 and previously published systematic reviews[28,29,76] suggest that corticosteroids may be beneficial in critically ill patients with severe sepsis, septic shock, and ARDS, the studies included in these analyses are limited by sample size and methodologic issues (*eg*, use of etomidate), and therefore, the risk-to-benefit ratio of stress-doses of corticosteroids should be assessed in each individual patient. However, based on current evidence, it would be reasonable to initiate treatment with stress-doses of corticosteroids in patients with vasopressor-dependent septic shock (norepinephrine or equ requirement $>$ 0.05 to 0.1 μg/kg/min) within 12 h of presentation and in patients with persistently severe ARDS who have failed to improve after 48 h of supportive care and a lung protective strategy (Table 3). A patient who requires only a few hours of low-dose vasopressor support while being fluid resuscitated is, however, unlikely to benefit from corticosteroids. While previous studies suggested that the decision to treat patients with septic shock should be based on the results of an ACTH stimulation test, the limitations of this test in diagnosing CIRCI and the benefit of corticosteroids in both responders and nonresponders suggest that this test should not be used to select patients likely to derive benefit from corticosteroids.[34] It is, however, unclear at this time whether dynamic testing of the HPA axis should be performed once patients have recovered from their acute illness and completed a course of corticosteroids to determine the normalization of the HPA axis. Furthermore, additional studies are required to determine whether the treatment of CIRCI improves long term mortality. It is possible that CIRCI is an epiphenomenon and a marker of illness severity, and that treatment with corticosteroids may alter the expression of inflammatory mediators and the severity of the inflammatory response without altering ultimate patient outcome.

Table 3—*Regimen for Corticosteroid Treatment in Critically Ill Patients*

Indications*
Vasopressor dependent septic shock (dosage of norepinephrine or equivalent $>$ 0.05 to 0.1 μg/kg/min) within 12 h of onset
or
Progressive ARDS after 48 h of supportive care
Dosing schedule
Hydrocortisone 50 mg IV every 6 h or 100-mg bolus then 10 mg/h continuous infusion for at least 7 d with option of treatment for 10 to 14 d. Patients should be vasopressor and ventilator "free" before taper
Hydrocortisone taper
Hydrocortisone 50 mg IV every 8 h for 3 to 4 d
Hydrocortisone 50 mg IV/po every 12 h for 3 to 4 d
Hydrocortisone 50 mg IV/po daily for 3 to 4 d
Reinstitution of full-dose hydrocortisone with recurrence of shock or worsening oxygenation
Fludrocortisone 50 μg po (optional)
Hydrocortisone and methylprednisone are considered interchangeable
Limiting complication of corticosteroid treatment
Infection surveillance: low threshold for performing blood cultures, mini-BAL. and other appropriate cultures
Hyperglycemia: monitor blood glucose, limit glycemic load, and treat with insulin as appropriate
Myopathy: monitor CPK and muscle strength, and avoid neuromuscular blocking agents

*A random cortisol or ACTH stimulation test is not required.

The use of etomidate as an anesthetic induction agent in critically ill patients is controversial, as this agent inhibits the 11β -hydroxylase enzyme that converts 11β -deoxycortisol into cortisol in the adrenal gland.[82] A single dose of etomidate has been demonstrated to inhibit cortisol production for up to 48 h, prompting the suggestion of steroid supplementation during this period.[83] Furthermore, etomidate was identified as an independent risk factor for death in the CORTICUS study (regardless of hydrocortisone or placebo treatment).[75]

The complications associated with the use of corticosteroids are dependent on the dose, the dosing strategy, and the duration of therapy. In the ICU setting (short-term treatment of CIRCI), the most important complications include immune suppression with an increased risk of infections (typical and opportunistic), impaired wound healing, hyperglycemia, myopathy, hypokalemic metabolic acidosis, psychosis, and HPA axis and GR suppression. The effect of glucocorticoids on immune suppression may be critically dose dependent. It is well know from the organ transplant experience that high-doses of corticosteroids effectively abolish T-cell mediated immune responsiveness and are very effective in preventing and/or treating graft rejection. Recent

studies, however, suggest that while stress-doses of corticosteroids inhibit systemic inflammation with decreased transcription of proinflammatory mediators, they maintain innate and Th1 immune responsiveness and prevent an overwhelming compensatory antiinflammatory response.[84,85] While the effects of corticosteroids on IL-10 and soluble TNF receptors is conflicting, corticosteroids should be avoided in chronically critically ill ICU patients with presumed compensatory antiinflammatory response.[84,86–89] Similarly, while myopathy is common in patients treated with high-dose corticosteroids, this complication is uncommon with stress doses of corticosteroids.[28,29]

Therefore, the literature does not support the use of high-dose corticosteroids in critically ill patients (except to prevent and/or treat rejection in transplant patients). This concept is supported by the increased mortality (25.7 vs 22.3%; $p = 0.0001$) of patients with head injuries in the MRC CRASH study who received methylprednisone in a dosage equivalent of 106,000 mg hydrocortisone for > 48 h.[90] Similarly, high doses of corticosteroids cannot be supported in patients with spinal cord injury[91–94]; physiologic-stress doses are very effective in reducing PLA2. PLA2 has been implicated in the secondary injury following spinal cord trauma.[95–97]

Previously, patients with septic shock have been treated for between 5 and 7 days, while patients with ARDS have been treated for up to 21 days. This difference does not appear logical as both conditions have in common systemic inflammation with immune dysregulation and high levels of proinflammatory mediators. Meduri et al[98] have demonstrated that persistent elevation of inflammatory cytokines predicts a poor outcome in patients with ARDS. In an observational study Briegel et al[99] noted a rebound of PLA2 in patients thought to have recovered from septic shock following 6 days of treatment with stress doses of hydrocortisone. Similarly in the CORTICUS study, the early weaning of hydrocortisone (after 5 days of treatment) was associated with a rebound of IL-6 (Didier Keh, MD; personal communication, May 2008) and a higher incidence of recurrent septic shock.[75] Recently, two longitudinal studies in patients with severe community acquired pneumonia found high levels of circulating inflammatory cytokines three weeks after clinical resolution of sepsis.[100,101] These data suggest that patients with severe sepsis and ARDS may have prolonged immune dysregulation (even after clinical recovery) and that a longer course of corticosteroids may be required. While clinical data to support this concept are lacking (excepting the experience with ARDS), treatment for up to 14 days (before tapering) should be considered in patients with an overwhelming systemic inflammatory response (Table 3).

The use of a continuous infusion of hydrocortisone has been reported to result in better glycemic control with less variability of blood glucose concentration and a reduction in the staff workload of managing hyperglycemia.[62,102–104] However, a continuous infusion of glucocorticoid may result in greater suppression of the HPA axis. In the sepsis studies, patients were treated with hydrocortisone, while methylprednisolone was the corticosteroid of choice in the ARDS studies. Different corticosteroids differentially effect gene transcription and have differing pharmacodynamic effects (John Cidlowski, MD; personal communication, May 2008). Consequently, the preferred corticosteroid as well as the optimal dosing strategy in critically ill patients with sepsis, ARDS, and other inflammatory states remains to be determined.

Abruptly stopping corticosteroids will likely result in a rebound of proinflammatory mediators with recurrence of the features of shock (and tissue injury).[78,84,99] In addition, it should be appreciated that glucocorticoid treatment itself results in down-regulation of GR levels and 11β -HSD-1, potentiating the rebound phenomenon following the abrupt cessation of glucocorticoid treatment.[105] A rapid steroid taper (> 2 to 6 days) as reported in the ARDSNet, CORTICUS, and Briegel studies was associated with rebound inflammation, increased levels of proinflammatory mediators (CORTICUS and Briegel studies), and the re-institution of vasopressor agents and/or mechanical ventilation.[75,78,99] The dosage of corticosteroids should, therefore, be incrementally reduced every 3 to 4 days with re-institution of full dosage with worsening oxygenation of recurrence of hypotension (Table 3).

In the study by Annane et al[32], patients in the treatment group received hydrocortisone together with fludrocortisone (50 μg po once daily). It is unclear if the addition of fludrocortisone played a role in the favorable outcome of this study. However, stress-doses of both hydrocortisone and methylprednisolone are believed to provide adequate mineralocorticoid activity, negating the need for fludrocortisone. Nevertheless, the benefit of the addition of fludrocortisone in patients with septic shock is currently being investigated in two RCTs comparing hydrocortisone alone vs hydrocortisone together with fludrocortisone (www.ClinicalTrial.gov, NCT 00368381 and NCT00320099). Treatment with fludrocortisone is considered optional at this time. Although treatment with dexamethasone has been suggested in patients with septic shock until an ACTH stimulation test is performed, this approach can no longer be endorsed. This recommendation is based on the fact that a single dose of a long-acting

corticosteroids may cause prolonged suppression of the HPA axis (limiting the value of ACTH testing).[106,107]

Additional Indications for Corticosteroids

RCTs have demonstrated the benefit of corticosteroids in patients with severe community acquire pneumonia, during weaning from mechanical ventilation, and in patients undergoing cardiac surgery.[31,108–113] In addition, observational studies suggest that stress doses of corticosteroids may have a role in the management of critically ill patients with liver disease.

Cardiac Surgery

Corticosteroids have been demonstrated to down-regulate activation of the proinflammatory cascade following cardiopulmonary bypass (CPB). The clinical benefits of corticosteroids (similar to those of sepsis and ARDS) may, however, be dose dependent. A number of studies noted an increase in the shunt fraction, greater hemodynamic instability, and a delay in extubation in patients undergoing CABG following the use of high-dose methylprednisolone.[114–116] However, Kilger et al[112] reported that the peri-operative use of physiologic stress-doses of hydrocortisone (100 mg before induction, 10 mg/h for 24 h followed by a taper) improved the outcome of a high-risk group of patients after cardiac surgery. Similarly, corticosteroids have been demonstrated to reduce the incidence of postoperative atrial fibrillation.[108–110]

Posttraumatic Stress Disorder

Corticosteroids are believed to play an important role in the post-traumatic stress disorder (PTSD) by influencing the consolidation or retrieval of traumatic memories. Patients with PTSD often show neuroendocrine system alterations such as increased urinary norepinephrine excretion and low plasma or urinary cortisol excretion.[117,118] Patients with low cortisol blood levels after a major motor vehicle accident have a high risk of developing PTSD during follow-up.[119,120] The administration of physiologic doses of hydrocortisone to critically ill patients with sepsis and following cardiac surgery results in a significant reduction of PTSD symptoms after recovery as well as improvements in health-related quality of life.[111,121,122] The mechanisms by which glucocorticoids improve PTSD may be a direct effect of glucocorticoids on neurotransmission; alternatively, the benefit may be due to the deceased use of catecholamines or the suppression of inflammatory mediators.

Liver Failure

Sepsis and end-stage liver disease have a number of patho-physiologic mechanisms in common (*eg*, endotoxemia, increased levels of proinflammatory mediators, and decreased levels of HDL), and it is, therefore, not surprising that adrenal insufficiency and CIRCI are common in patients with end-stage liver disease.[55,123,124] Tsai et al[125] performed a corticotrophin stimulation test in 101 patients with cirrhosis and sepsis. In this study 51.4% of the patients were diagnosed with adrenal insufficiency; survival at 90 days was 15.3% in these patients in comparison to 63.2% in patients with normal adrenal function. None of the patients were treated with corticosteroids. Fernandez et al[126] compared the survival of patients with cirrhosis and sepsis who underwent adrenal function testing in which patients with adrenal insufficiency were treated with hydrocortisone (group 1) to survival in a control group (group 2) that did not undergo cosyntropin testing and were not treated with corticosteroids. The incidence of adrenal failure was 68% in group 1, and the hospital survival was 64% in group 1 and only 32% in group 2 ($p = 0.003$). We recently reported the results of the Hepatic Cortisol Research and Adrenal Pathophysiology Study in which 245 of 340 (72%) critically ill patients with liver disease were diagnosed with adrenal insufficiency (the Hepato-Adrenal Syndrome).[127] These data suggest that adrenal dysfunction and CIRCI are common in critically ill patients with end-stage liver disease and that treatment with corticosteroids may improve outcome.

Conclusion

Critical illness-related corticosteroid insufficiency (CIRCI) is a complex disease, and our understanding of this disease continues to evolve. In critically ill patients with catecholamine refractory septic shock and patients with persistent severe ARDS for > 48 h after supportive therapy, a course of stress-dose corticosteroids (200 to 350 mg/d of hydrocortisone or 40 to 70 mg/d of methylprednisolone) should be considered. Treatment for at least 7 days (and up to 14 days) is suggested, followed by a slow taper. These recommendations are based on limited data, and addition studies are therefore required.

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