

Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine

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Objective: To develop consensus statements for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients.

Participants: A multidisciplinary, multispecialty task force of experts in critical care medicine was convened from the membership of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. In addition, international experts in endocrinology were invited to participate.

Design/Methods: The task force members reviewed published literature and provided expert opinion from which the consensus was derived. The consensus statements were developed using a modified Delphi methodology. The strength of each recommendation was quantified using the Modified GRADE system, which classifies recommendations as strong (grade 1) or weak (grade 2) and the quality of evidence as high (grade A), moderate (grade B), or low (grade C) based on factors that include the study design, the consistency of the results, and the directness of the evidence.

Results: The task force coined the term **critical illness-related corticosteroid insufficiency** to describe the dysfunction of the hypothalamic-pituitary-adrenal axis that occurs during critical illness. Critical illness-related corticosteroid insufficiency is caused by adrenal insufficiency together with tissue corticosteroid resistance and is characterized by an exaggerated and protracted proinflammatory response. Critical illness-related corticosteroid insufficiency should be suspected in hypotensive patients who have responded poorly to fluids and vasopressor agents, particularly in the setting of sepsis. At this time, the diagnosis of tissue corticosteroid resistance remains problematic. Adrenal insufficiency in critically ill patients is best made by a delta total serum cortisol of $<9 \mu\text{g/dL}$ after adrenocorticotropic

hormone (250 μg) administration or a random total cortisol of $<10 \mu\text{g/dL}$. The benefit of treatment with glucocorticoids at this time seems to be limited to patients with vasopressor-dependent septic shock and patients with early severe acute respiratory distress syndrome ($\text{Pao}_2/\text{Fio}_2$ of <200 and within 14 days of onset). The adrenocorticotropic hormone stimulation test should not be used to identify those patients with septic shock or acute respiratory distress syndrome who should receive glucocorticoids. Hydrocortisone in a dose of 200 mg/day in four divided doses or as a continuous infusion in a dose of 240 mg/day (10 mg/hr) for ≥ 7 days is recommended for septic shock. Methylprednisolone in a dose of 1 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ for ≥ 14 days is recommended in patients with severe early acute respiratory distress syndrome. Glucocorticoids should be weaned and not stopped abruptly. Reinstitution of treatment should be considered with recurrence of signs of sepsis, hypotension, or worsening oxygenation. Dexamethasone is not recommended to treat critical illness-related corticosteroid insufficiency. The role of glucocorticoids in the management of patients with community-acquired pneumonia, liver failure, pancreatitis, those undergoing cardiac surgery, and other groups of critically ill patients requires further investigation.

Conclusion: Evidence-linked consensus statements with regard to the diagnosis and management of corticosteroid deficiency in critically ill patients have been developed by a multidisciplinary, multispecialty task force. (Crit Care Med 2008; 36:1937-1949)

Key Words: corticosteroid; glucocorticoid; insufficiency; deficiency; adult; adrenal glands; diagnosis; management; consensus statement; guidelines; Delphi methodology; evidence-based medicine; sepsis; cortisol; critical care; intensive care units; intensive care; shock septic; surgery; stress dosing

*See also p. 1987.

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The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

Dr. Marik has received lecture fees from Eli Lilly and Merck. Dr. Keh has received grant support from the German Research Foundation and German Ministry of Education and Research (HYPRESS: Hydrocortisone for Prevention of Septic Shock). Dr. Sprung has been a member of a data monitoring and safety committee for Artisan Pharma, Novartis Corporation, and Hutchinson Technology Incorporated. He has served as a consultant for AstraZeneca, Eisai Corporation, Eli Lilly, and GlaxoSmithKline. He has received grant support from the European Commission, Takeda, and Eisai Corporation. He has received lecture fees from Eli Lilly. Drs. Sprung, Annane, Keh, Singer, and Briegel were investigators in the CORTICUS study, which was supported by the European Commission, the European Society of Intensive Care Medi-

cine, the European Critical Care Research Network, the International Sepsis Forum, and the Gorham Foundation. Dr. Annane has received grant support from the French Ministry of Health for the prognostic value of an adrenocorticotropic hormone test in septic shock; the French multicenter, randomized, controlled trial on hydrocortisone plus fludrocortisone in septic shock; the ongoing French multicenter 2×2 factorial study that compares strict glucose control vs. conventional treatment for steroid-treated septic shock and hydrocortisone alone vs. hydrocortisone and fludrocortisone; and a French multicenter 2×2 factorial trial that compares hydrocortisone plus fludrocortisone, activated protein C, the combination of the two drugs, and placebos for the treatment of septic shock. Dr. Pastores has received grant support from Eisai Medical Research (phase 3 trial of E5564 in severe sepsis), and Artisan Pharma (phase 2 sepsis with disseminated intravascular coagulation trial). The remaining authors have not disclosed any conflicts of interest with respect to this article.

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DOI: 10.1097/CCM.0b013e31817603ba

Severe illness and stress strongly activate the hypothalamic-pituitary-adrenal (HPA) axis and stimulate the release of adrenocorticotrophic hormone (ACTH) from the pituitary, which in turn increases the release of cortisol from the adrenal cortex (1–3). This activation is an essential component of the general adaptation to illness and stress and contributes to the maintenance of cellular and organ homeostasis. Adrenalectomized animals succumb rapidly to hemorrhagic and septic shock, and steroid replacement is protective against these challenges (4, 5).

Once considered a rare diagnosis in the intensive care unit, “adrenal failure” is being reported with increasing frequency in critically ill patients with septic shock, severe community-acquired pneumonia, trauma, head injury, burns, liver failure, HIV infection, pancreatitis, after cardiac surgery, after the use of etomidate, and in brain-dead organ donors (6–11). Adrenal failure may be associated with structural damage to the adrenal gland, pituitary gland, or hypothalamus; however, many critically ill patients develop reversible failure of the HPA axis.

Although it is generally agreed that adrenal failure may be common in subgroups of critically ill patients, the diagnosis and management of this disorder remains controversial, with poor agreement among the experts. The objective of this task force was therefore to develop consensus statements by experts in the field based on the best available scientific evidence (12).

METHODS

Experts were selected from the membership lists of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ES-ICM). Specific individuals were selected to represent geographic diversity and a broad range of expertise on the basis of their published research. In addition, endocrinologists with expertise in this area were invited to join the task force.

The consensus statement was developed using a modified Delphi methodology (12). The Delphi method, originally developed by the RAND Corporation, is a structured process that uses a series of questionnaires, each referred to as a round, to both gather and provide information (13, 14). With each round, the answers are modified based on the responses of the previous round. The

rounds continued until a group consensus or majority is reached. This approach has several distinct advantages. It allows the inclusion of a large number of individuals across diverse geographic locations and with a broad range of expertise. One of its key advantages is that unlike a face-to-face meeting of experts, it eliminates the possibility that a specific expert might dominate the consensus process. The Delphi method helps to minimize the effects of group interactions and maximizes the ability to elicit expert knowledge.

The task force members individually and collectively undertook a systematic search of published literature pertaining to the diagnosis and treatment of adrenal failure in critically ill adult patients using Medline, CINAHL, EMBASE, and the Cochrane library. In addition, the reference lists of relevant articles were reviewed for additional published works. Key words used in these searches included “pituitary–adrenal system, adrenal insufficiency, adrenal glands, pituitary–adrenal function tests, hydrocortisone, glucocorticoids (GC), adrenal cortex hormones, glucocorticoid receptor (GR), critical care, intensive care units, intensive care, ARDS, shock septic, sepsis, and sepsis syndrome.” A comprehensive bibliography was developed, with the references stored and cataloged using an electronic reference manager (Reference Manager v11.1, Thompson ResearchSoft, Carlsbad, CA).

We used electronic mail to conduct the Delphi process. A list of questions for review was determined. Once a majority agreement was reached on each question, the strength of each recommendation was quantified using the Modified Grades of Recommendation Assessment, Development, and Evaluation (GRADE) system developed by the American College of Chest Physicians (Appendix 1) (15). In all, there were seven rounds until a majority agreement was achieved on all the questions. In addition, the group met in Paris, France, in September 2005 and again at the Society of Critical Care Medicine 35th Critical Care Congress in San Francisco, CA, in January 2006 to review the progress of the Delphi process. The initial draft of the manuscript was written by the Chair (P. E. Marik). The draft manuscript was reviewed and iteratively edited by all members of the task force.

A meta-analysis of randomized controlled trials that compared the 28-day mortality and vasopressor dependency of patients with septic shock and the 28-day

mortality of patients with acute respiratory distress syndrome (ARDS) who received either moderate-dose corticosteroid or placebo was performed. Four of the task force members (P. E. Marik, D. Annane, S. M. Pastores, G. U. Meduri) reviewed the task force bibliography for relevant studies. Septic shock was defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference and ARDS by the American–European Consensus Conference (16, 17). Vasopressor dependency was defined as the requirement for a vasopressor agent after 7 days of treatment with a glucocorticoid (GC). The reviewers independently abstracted data from all eligible studies. Data were abstracted on study design, study size, corticosteroid dosage, vasopressor dependency, and 28-day mortality. Study and data inclusion was by consensus. We used the random effects models using Review Manager 4.2 (Cochrane Collaboration, Oxford, UK) for all analyses and considered $p < .05$ (two-sided) as significant. Summary effects estimates are presented as odds ratio with 95% confidence intervals. We assessed heterogeneity between studies using the Cochran Q statistic with $p < .10$ indicating significant heterogeneity and the I^2 with suggested thresholds for low (25–49%), moderate (50–74%), and high (>75%) values (18–21).

BACKGROUND

Exposure to hostile conditions results in a series of coordinated responses—often referred to as *stress responses*—organized to enhance survival; these include a series of complex central and peripheral adaptations. This stress response is mediated mainly by the HPA axis and the sympathoadrenal system, which includes the sympathetic nervous system and the adrenal medulla (Fig. 1) (22–24). The HPA axis and the sympathoadrenal system are functionally related. Activation of the sympathoadrenal system results in the secretion of epinephrine and norepinephrine from the adrenal medulla and also leads to an increased production of inflammatory cytokines, such as interleukin-6. Activation of the HPA axis results in increased secretion from the paraventricular nucleus of the hypothalamus of corticotropin-releasing hormone, a 41-amino acid peptide, and arginine vasopressin. Corticotropin-releasing hormone plays a pivotal integrative role in the response to stress.

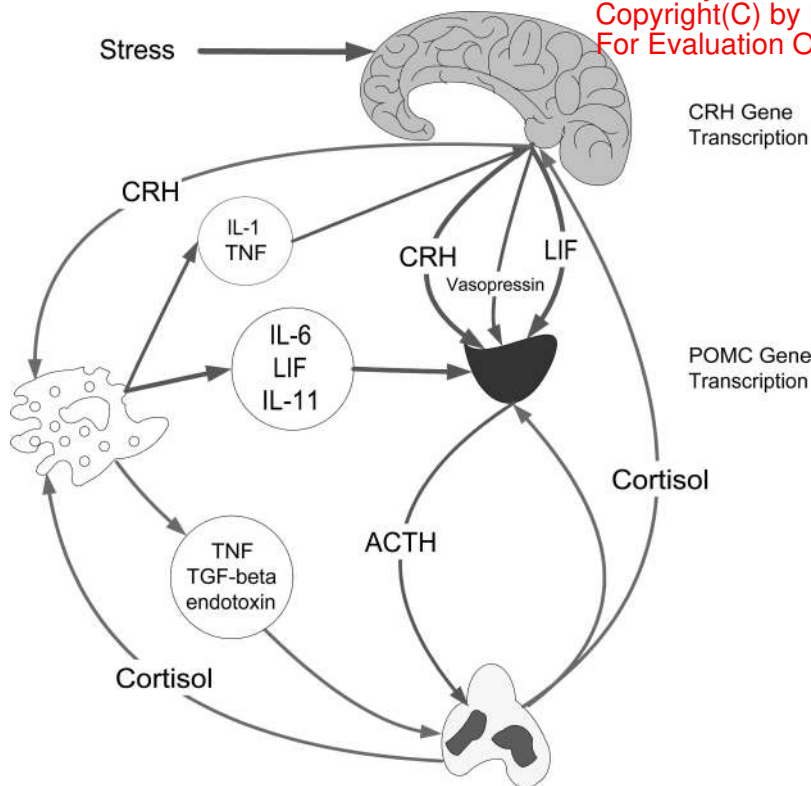


Figure 1. Activation of the hypothalamic-pituitary-adrenal axis by a stressor and the interaction with the inflammatory response. *ACTH*, adrenocorticotrophic hormone; *CRH*, corticotropin-releasing hormone; *IL-6*, interleukin-6; *IL-11*, interleukin-11; *LIF*, leukemia inhibitory factor; *POMC*, proopiomelanocortin; *TGF-beta*, transforming growth factor- β ; *TNF*, tumor necrosis factor.

Corticotropin-releasing hormone stimulates the production of ACTH by the anterior pituitary, causing the zona fasciculata of the adrenal cortex to produce more GCs (cortisol in humans, corticosterone in rats). Arginine vasopressin is a weak ACTH secretagogue and vasoactive peptide that acts synergistically with corticotropin-releasing hormone to increase secretion of ACTH. The increase in cortisol production results in multiple effects (metabolic, cardiovascular, and immune) aimed at maintaining or restoring homeostasis during stress.

Cortisol Physiology, Synthesis, and Glucocorticoid Receptors

Cortisol is the major endogenous GC secreted by the adrenal cortex. More than 90% of circulating cortisol is bound to corticosteroid-binding globulin, with <10% in the free, biologically active form (25, 26). Corticosteroid-binding globulin is the predominant binding protein, with albumin binding a lesser amount. During acute illness, particularly sepsis, corticosteroid-binding globulin levels fall by as much as 50%, result-

ing in a significant increase in the percentage of free cortisol (27, 28). The circulating half-life of cortisol varies from 70 to 120 mins. The adrenal gland does not store cortisol; increased secretion arises due to increased synthesis under the control of ACTH (29). 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, dehydroepiandrosterone, and cortisol (29). 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 (30). Experimental studies suggest that high-density lipoprotein is the preferred cholesterol source of steroidogenic substrate in the adrenal gland (31). Recently, mouse SR-B1 (scavenger receptor, class B, type 1) and its human homolog (Cla-1) have been identified as the high-affinity high-density lipoprotein

receptor mediating selective cholesterol uptake (32–34). 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 (35).

Cortisol exerts its effects after uptake from the circulation by binding to intracellular glucocorticoid receptors (GRs) (3). 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 GR in the cytoplasm results in the activation of the steroid receptor complex via a process involving the dissociation of heat shock proteins (heat shock proteins 90 and 70) and FK-506 binding proteins (36–38). Intracellularly, the cortisol-GR 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-GR complex may affect cellular function indirectly by binding to and modulating the transcriptional activity of other nuclear transcription factors, such as nuclear factor κ B (NF- κ B) and activator protein-1. Overall, GCs affect the transcription of thousands of genes in every cell of the body. It has been estimated that GCs affect 20% of the genome of mononuclear blood cells (39).

GCs play a major role in regulating the activity of NF- κ B, which plays a crucial and generalized role in inducing cytokine gene transcription (40–42). NF- κ B is normally maintained in an inactive form by sequestration in the cytoplasm through interaction with inhibitory proteins (I κ Bs). On stimulation by lipopolysaccharide, double-stranded DNA, physical and chemical stresses, and inflammatory cytokines, the latent NF- κ B/I κ B complex is activated by phosphorylation and proteolytic degradation of I κ B, with exposure of the NF- κ B nuclear localization sequence. The liberated NF- κ B then translocates to the nucleus and binds to promoter regions of target genes to initiate the transcription of multiple cytokines (including tumor necrosis factor- α , interleukin-1, and interleukin-6), cell adhesion molecules (e.g., intercellular adhesion molecule-1, E-selectin), and other mediators of inflammation.

GCs inhibit the activity of NF- κ B by increasing the transcription of I κ Bs and by directly binding to and inhibiting NF- κ B (41, 42).

Cortisol has several important physiologic actions on metabolism, cardiovascular function, and the immune system (6, 43). The metabolic effects of cortisol include an **increase in blood glucose concentrations** through the activation of key enzymes involved in hepatic gluconeogenesis and inhibition of glucose uptake in peripheral tissues such as the skeletal muscles. In addition, 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, increasing glucose levels, including catecholamines and glucagon. Sustained cortisol hypersecretion stimulates glucose production at the expense of protein and lipid catabolism and insulin resistance.

Cortisol increases blood pressure through several mechanisms involving the kidney and vasculature. In vascular smooth muscle, **cortisol increases sensitivity to vasopressor agents such as catecholamines and angiotensin II** (44, 45). These effects are mediated partly by the increased transcription and expression of the receptors for these hormones (44, 45). Although the effect of GCs on nitric oxide is complex, **it seems to increase endothelial nitric oxide synthetase**, thereby maintaining microvascular perfusion (46–49). Cortisol has potent anti-inflammatory actions, including the reduction in the number and function of various immune cells, such as T and B lymphocytes, monocytes, neutrophils, and eosinophils, at sites of inflammation. Cortisol decreases the production of cytokines, chemokines, and eicosanoids and enhances the production of macrophage migration inhibitory factor (22, 50).

Dysfunction of the HPA Axis During Acute Illness

The acute stress response during critical illness is characterized by activation of the HPA and sympathoadrenal system axis, with increased secretion of cortisol, an increase in the percentage of free cortisol, and increased translocation of the GR complex into the nucleus. Importantly, there is increasing evidence that in many critically ill patients, this pathway may be impaired (27, 51, 52). The reported prevalence of adrenal insufficiency in critically ill patients varies

widely (0–77%), depending on the population of patients studied and the diagnostic criteria. However, the overall prevalence of adrenal insufficiency in critically ill medical patients approximates 10–20%, with a rate as high as 60% in patients with septic shock. In a study recently published by Annane et al. (53), the **prevalence of adrenal insufficiency (as determined by metyrapone testing) in patients with severe sepsis and septic shock was reported to be 60%**. The major effect of adrenal insufficiency in the critically ill patient is manifested through alterations in the systemic inflammatory response and cardiovascular function.

The mechanisms leading to dysfunction of the HPA axis during critical illness are complex and poorly understood and likely include decreased production of corticotropin-releasing hormone, ACTH, and cortisol and the dysfunction of their receptors. A subset of patients may have 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, after major surgery, in disseminated intravascular coagulation associated with sepsis, and in patients with burns, heparin-induced thrombocytopenia, the antiphospholipid syndrome, HIV infection, disseminated fungal infections, and tuberculosis** (3, 54–59). In addition, patients who have been treated long term with adrenally suppressive doses of exogenous GCs are likely to develop secondary adrenal insufficiency (3, 6). However, it seems that most critically ill patients who develop adrenal insufficiency develop reversible dysfunction of the HPA axis (6, 60). Decreased production of cortisol or ACTH is particularly common in patients with **severe sepsis and septic shock** (60). Annane et al. (53) demonstrated an increased risk of adrenal insufficiency in patients with **positive blood cultures and those with Gram-negative infections**.

Clinical and experimental data indicate that the failure to improve in sepsis and ARDS is frequently associated with failure of activated GRs to down-regulate the transcription of inflammatory cytokines, despite elevated levels of circulating cortisol, a condition defined as *systemic inflammation-associated GC resistance* (61). Tissue corticosteroid resistance is a well-known manifestation of chronic inflammatory diseases, such as chronic obstructive pulmonary disease,

severe asthma, systemic lupus erythematosus, ulcerative colitis, and rheumatoid arthritis (62–65). It is therefore likely that acute inflammation, similar to chronic inflammation, may be associated with tissue corticosteroid resistance (61). In experimental models, endotoxin and proinflammatory cytokines have been shown to cause decreased GR nuclear translocation (66–68). In an *ex vivo* model, Meduri et al. (69) **demonstrated reduced nuclear translocation of the GR complex in patients with fatal ARDS**, despite adequate cytoplasmic (and serum) levels of cortisol. It is likely that multiple mechanisms cause systemic inflammation-associated GC resistance, including decreased GR number, increased expression of the beta isoform of the GR (unable to bind ligand), altered ratio of chaperone proteins (FK binding proteins and heat shock protein 90), reduced affinity of the GR for ligand, altered nuclear receptor coactivators, reduced DNA binding, decreased histone acetylation, increased activity of the P-glycoprotein membrane transport pump, and increased conversion of cortisol to cortisone (61, 68, 70–72). Furthermore, polymorphisms of the GR and other pivotal genes may influence the downstream effects of the GC–GR interaction (73, 74). Additional research in this area, particularly as it applies to critically ill patients, is urgently required.

Current evidence suggests that mediators released in patients with critical illness, and sepsis in particular, may either stimulate or impair the synthesis and action of cortisol via actions on the HPA axis and the GR signaling system. The net effect of these opposing actions on the HPA axis and GR may be time dependent and, in addition, depend on the severity of illness and the extent and pattern of mediator production. Although the focus on most research has been in the area of sepsis and ARDS, it is likely that similar mechanisms operate in other disorders characterized by significant systemic inflammation, including **pancreatitis, burns, post-cardiopulmonary bypass, and liver failure** (75–79).

RECOMMENDATIONS OF THE TASK FORCE

Critical Illness–Related Corticosteroid Insufficiency

Recommendation 1: Dysfunction of the HPA axis in critical illness is best described by the term **critical illness–**

related corticosteroid insufficiency (CIRCI).

Recommendation 2: The terms *absolute* or *relative* adrenal insufficiency are best avoided in the context of critical illness.

Dysfunction of the HPA axis in critical illness is best described by the term *critical illness-related corticosteroid insufficiency* (CIRCI). CIRCI is defined as inadequate cellular corticosteroid activity for the severity of the patient's illness. CIRCI manifests with insufficient GC-GR-mediated down-regulation of proinflammatory transcription factors, leading to persistent elevation of proinflammatory mediators over time. CIRCI occurs as a result of a decrease in adrenal steroid production (adrenal insufficiency) or tissue resistance to GCs (with or without adrenal insufficiency). Adrenal insufficiency may arise due to dysfunction at any point in the HPA axis. The terms *absolute* or *relative* adrenal insufficiency are best avoided in the context of critical illness (80). CIRCI is a dynamic process (i.e., patients may not have CIRCI at admission to the hospital/intensive care unit but may develop CIRCI during the course of their illness) (81–83). CIRCI is usually a reversible condition caused by proinflammatory mediators; however, it may also arise due to structural damage of the adrenal gland. CIRCI may affect the balance between proinflammatory and anti-inflammatory pathways and thereby influence immune, metabolic, vascular, and organ dysfunction.

Diagnosis of Adrenal Insufficiency

Recommendation 3: At this time, adrenal insufficiency in critical illness is best diagnosed by a delta cortisol (after 250 μg cosyntropin) of $<9 \mu\text{g/dL}$ or a random total cortisol of $<10 \mu\text{g/dL}$.

Strength of Recommendation: 2B

Recommendation 4: The use of free cortisol measurements cannot be recommended for routine use at this time. Although the free cortisol assay has advantages over the total serum cortisol, this test is not readily available. Furthermore, the normal range of the free cortisol in critically ill patients is currently unclear.

Strength of Recommendation: 2B

Recommendation 5: The ACTH stimulation test should not be used to identify those patients with septic shock or ARDS who should receive GCs.

Strength of Recommendation: 2B

The diagnosis of adrenal insufficiency in critically ill patients 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 μg of synthetic ACTH (ACTH stimulation test), the so-called delta cortisol (6, 84). Both of these tests have significant limitations in the critically ill (85). Assays for serum cortisol measure the total hormone concentration (serum-free cortisol plus the protein-bound fraction). The consensus is that the free cortisol, rather than the protein-bound fraction, is responsible for the physiologic function of the hormone at the cellular level (6, 50, 86). In most critically ill patients, corticosteroid-binding globulin levels are decreased and the percentage of free cortisol is increased (27, 51, 52, 86, 87). Furthermore, with acute stimulation of the adrenal gland, the relative increase of free bioactive cortisol concentrations is substantially more pronounced than the increase of total cortisol concentrations (27, 51, 52, 86–88). Consequently, in critically ill patients, the total serum cortisol level may not accurately reflect the free cortisol level. This dissociation between the total and free cortisol level is most marked in patients with a serum albumin of $<2.5 \text{ mg/dL}$ (85, 87, 89).

Although measurement of the free cortisol level may arguably be preferable, this test is currently not widely available. It is likely, however, that with improvement in laboratory techniques and clinical demand, this test will become commercially available (90). The interpretation of the total serum cortisol concentration is further complicated by the fact that the specificity, sensitivity, and performance of the commercially available assays are not uniform (91). It is likely that the variation in assay characteristics might be even more significant in critically ill patients, especially those with septic shock (91, 92). Cross-reactivity of the cortisol immunoassay with precursors or metabolites of cortisol that accumulate in sepsis may account for this observation.

Although a delta cortisol of $<9 \mu\text{g/dL}$ has proven to be an important prognostic marker (9, 53, 93, 94), and a marker of response to treatment with corticosteroids (95, 96), the ACTH stimulation test has a number of limitations. The delta cortisol is a measure of the ability of the

adrenal gland to increase production of cortisol in response to ACTH; it does not assess the integrity of the HPA axis, the response of the HPA axis to other stresses (i.e., hypotension, hypoglycemia), or the adequacy of stress cortisol levels. In addition, the ACTH stimulation test may be poorly reproducible, especially in patients with septic shock (97, 98). Despite these limitations, Annane et al. (53) have reported that a delta cortisol of $<9 \mu\text{g/dL}$ and a random total cortisol of $<10 \mu\text{g/dL}$ were the best predictors of adrenal insufficiency (as determined by metyrapone testing) in patients with severe sepsis/septic shock. Furthermore, although the 1- μg ACTH stimulation test may be more physiologic and have a greater sensitivity than the 250- μg test, due to limited data, the 1- μg test dose is currently not recommended (99). It should also be appreciated that at present, we are unable to measure tissue GC resistance or determine the circulating cortisol level that is required to overcome tissue resistance.

In those patients (severe sepsis, septic shock, and ARDS) most likely to benefit from treatment with moderate-dose GCs, it is not clear that treatment should be based on the results of adrenal function testing. To date, six randomized, placebo-controlled studies have evaluated hydrocortisone treatment (200–300 mg/day) in patients with septic shock (95, 100–103) (Figs. 2 and 3). In these studies, more rapid shock reversal was noted in patients treated with hydrocortisone, and this benefit was noted in both ACTH responders (delta cortisol of $>9 \text{ mg/dL}$) and non-responders (delta cortisol of $<9 \text{ mg/dL}$) (Fig. 2). Furthermore, recent randomized controlled studies in patients with early ARDS (treatment within 14 days) and severe community-acquired pneumonia demonstrated improved outcome with GCs (when compared with placebo), independent of adrenal function testing (see section below) (7, 104, 105). These data suggest that in patients with septic shock and early ARDS, the decision to treat with moderate-dose corticosteroids should be based on clinical criteria and not on the results of adrenal function testing. The inability to diagnose corticosteroid tissue resistance may partly explain these observations.

Who to Treat with Glucocorticoids?

Recommendation 6: Hydrocortisone should be considered in the management strategy of patients with septic shock, particularly those patients who

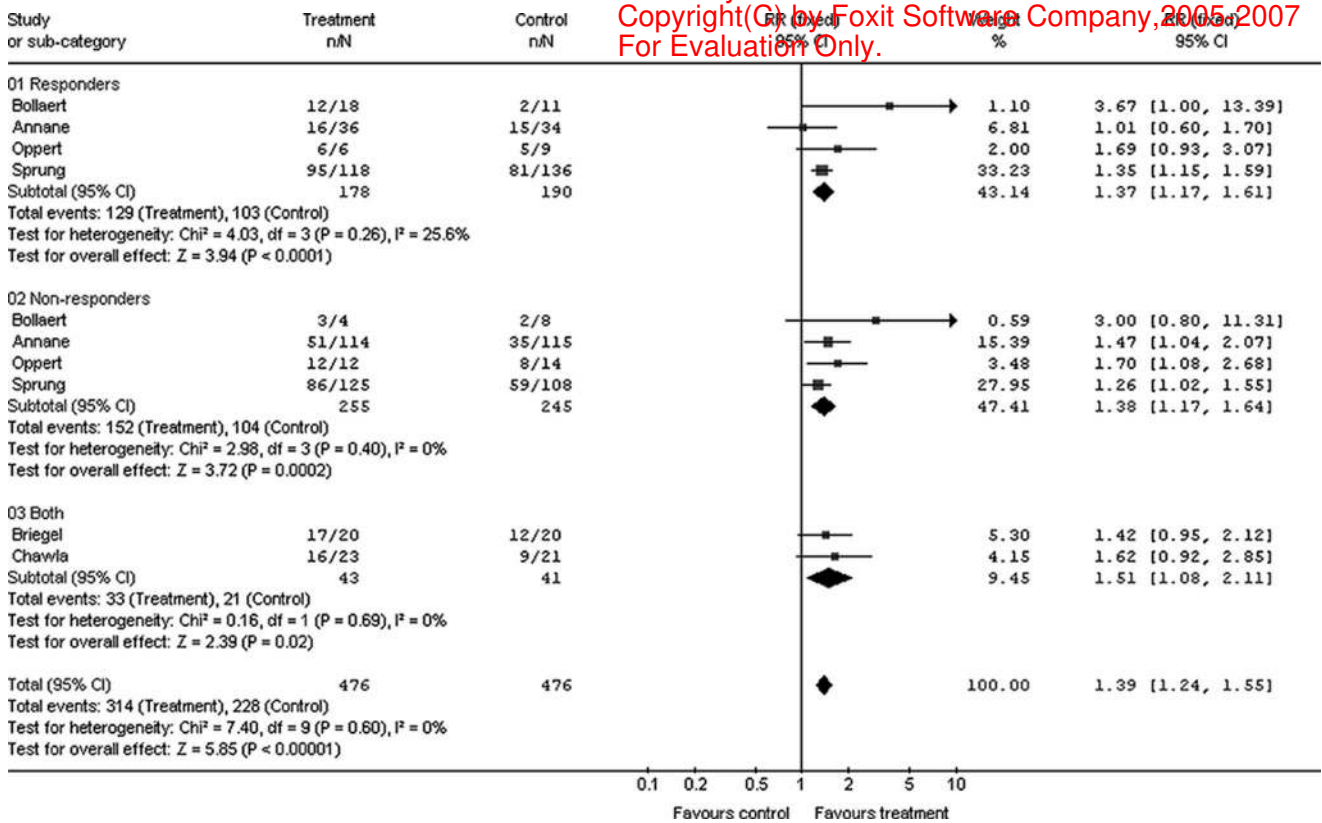


Figure 2. Meta-analysis of treatment with moderate-dose hydrocortisone on shock reversal at day 7 in patients with septic shock grouped by response to adrenocorticotrophic hormone. RR, relative risk; 95% CI, 95% confidence interval.

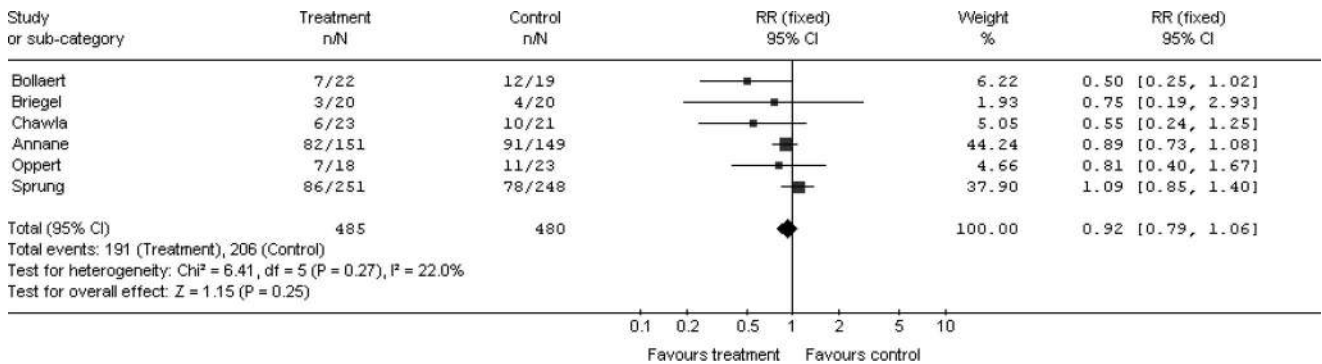


Figure 3. Meta-analysis of treatment with moderate-dose hydrocortisone on 28-day survival in patients with septic shock. RR, relative risk; 95% CI, 95% confidence interval.

have responded poorly to fluid resuscitation and vasopressor agents.

Strength of Recommendations: 2B

The benefit of moderate-dose hydrocortisone (200–300 mg/day) in patients with septic shock has been evaluated in six randomized controlled trials (95, 100–103, 106). A meta-analysis of these six studies (including the recently completed CORTICUS study) demonstrates greater shock reversal (at day 7) with hydrocortisone but no benefit in terms of mortality (Figs. 2 and 3). The variability

in study size, inclusion criteria, and corticosteroid dosing limits the interpretation of this meta-analysis. Nevertheless, the French multicenter study and the recently completed European multicenter study (CORTICUS) were better powered to detect a survival difference and deserve further analysis. Annane et al. (95) randomized 300 patients with refractory septic shock (systolic blood pressure of <90 mm Hg for >1 hr, despite fluid resuscitation and the use of vasopressor agents) to treatment with hydrocortisone (50 mg intravenously every 6 hrs) and oral

fludrocortisone (50 µg daily) or matching placebo for 7 days. All patients underwent an ACTH stimulation test. There was a 30% decrease in 28-day mortality in the hydrocortisone-fludrocortisone group (hazard ratio, 0.67; 95% confidence interval, 0.47–0.95; $p = .02$) (95). This benefit was confined to the group of nonresponders (delta cortisol of <9 µg/dL).

The CORTICUS study was a double-blind, randomized, placebo-controlled study performed in 52 centers throughout Europe (106). A total of 500 patients (499 available to analyze) were enrolled

between March 2002 and November 2005. Inclusion criteria included septic shock (systolic blood pressure of <90 mm Hg, despite adequate fluid resuscitation or need for vasopressors) and evidence of organ dysfunction attributable to sepsis. Patients were randomized to hydrocortisone (50 mg intravenously every 6 hrs for 5 days, then 50 mg intravenously every 12 hrs for 3 days, followed by 50 mg intravenously daily for 3 days) or matching placebo. Patients did not receive fludrocortisone. Although the baseline characteristics of the patients were similar, only 35% of the cohort were medical patients, with the abdomen being the commonest source of infection (48%). There was no difference in the 28-day all-cause mortality between those patients who received hydrocortisone as compared with placebo. Furthermore, there was no difference in mortality between the groups when stratified as responders (delta cortisol of >9 µg/dL) or nonresponders (delta cortisol of <9 µg/dL) to the ACTH stimulation test. However, the patients who received hydrocortisone had more rapid resolution of shock ($p = .001$ for responders and $p = .06$ for nonresponders). There were, however, more episodes of new infection (not statistically significant) and septic shock (rebound inflammation) in the hydrocortisone group. The prevalence of other adverse events, including critical illness polyneuropathy, was similar between groups.

A number of factors may account for the different results of the French multicenter study and the CORTICUS study. The patients enrolled in the French study were sicker than those enrolled in the CORTICUS study (28-day mortality in the placebo arm of 61% vs. 31.5%). Furthermore, the time window of enrollment was 8 hrs in the French study as compared with 72 hrs in the CORTICUS study. It is likely that only patients at a high risk of death will benefit from corticosteroids, and this benefit may diminish with a de-

lay in instituting treatment. It is also possible that improvements in the supportive care of critically ill patients with septic shock over the last decade have increased the survival of patients with CIRCI who would otherwise have died. The demographics and clinical characteristics of the patients enrolled in the two studies were quite different, with 40.1% of patients in the French study being surgical patients as compared with 64.5% in the CORTICUS study. Source control may be more important in determining the outcome of sepsis in surgical patients than that of adjunctive interventions. Furthermore, it is possible that selection bias affected the demographics and outcome of the CORTICUS study. Although it has been suggested that clinical equipoise existed during enrollment into the CORTICUS study (107), many intensivists continue to use corticosteroids in the management of patients with septic shock (108, 109).

Given the different outcomes of the French and CORTICUS studies, what should the clinician do? Considering the central role of cortisol in modulating the stress response and recognizing the potential suppressive effects of sepsis on the HPA axis and on GR activity, the use of moderate-dose hydrocortisone seems rational in patients with septic shock poorly responsive to fluid and vasopressor resuscitation. This is supported by recent data that demonstrate that up to 60% of patients with severe sepsis and septic shock have adrenal insufficiency (53). The best available clinical evidence suggests that moderate-dose hydrocortisone results in significantly more rapid resolution of shock (Fig. 2). The effects of moderate-dose hydrocortisone on mortality seem less clear (Fig. 3). Nevertheless, based on current data, hydrocortisone should be considered in the management strategy of patients with septic shock, particularly those patients who have responded poorly to fluid resuscitation and vasopressor agents. As noted in Figure 2, more rapid

resolution of shock was noted in both responders and nonresponders. Thus, at this time, it seems that the decision to treat patients with septic shock should not be based on the results of a random total cortisol level or the response to ACTH. In addition, it should be noted that the administration of hydrocortisone during septic shock has been demonstrated to reduce the prevalence of post-traumatic stress disorder and improve the emotional well-being of survivors of septic shock (110).

Recommendation 7: Moderate-dose GC should be considered in the management strategy of patients with early severe ARDS (PaO_2/FiO_2 of <200) and before day 14 in patients with unresolved ARDS. The role of GC treatment in acute lung injury and less severe ARDS (PaO_2/FiO_2 of >200) is less clear.

Strength of Recommendations: 2B

Five randomized studies ($n = 518$) have evaluated the role of GC treatment in patients with acute lung injury due to community-acquired pneumonia (7) and in patients with ARDS of varied origins (104, 105, 111, 112). Varying doses (200–750 mg of hydrocortisone equivalents per day), dosing strategies (infusion/bolus), and duration of therapy (7–32 days) were used in these studies. Due to the marked differences in study design and patient characteristics, the cumulative summary of these studies should be interpreted with some caution. Nevertheless, these trials consistently reported that treatment was associated with significant improvement in PaO_2/FiO_2 (7, 104, 105, 111, 112), a significant reduction in markers of systemic inflammation (7, 104, 105, 111, 112), duration of mechanical ventilation (7, 104, 105, 111, 112), and intensive care unit length of stay (all with p values of <.05) (7, 104, 105, 111). Subgroup analysis (Fig. 4) based on studies that investigated only treatment (methyl-

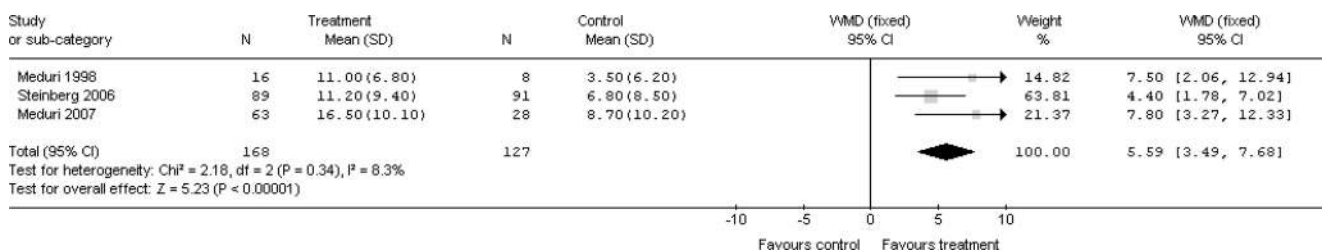


Figure 4. Effects of prolonged methylprednisolone treatment on mechanical ventilation-free days at day 28. Reproduced with permission from Meduri et al (114). WMD, weighted mean difference; 95% CI, 95% confidence interval.

prednisolone) durations of >1 wk (n = 295) (104, 105, 111) showed a distinct increase in the number of mechanical ventilation-free days (weighted mean difference, 5.59 days; 95% confidence interval, 3.49–7.68; *p* < .001).

GC treatment in acute lung injury-ARDS was not associated with increased rates of gastrointestinal bleeding or nosocomial infections, and two of the studies reported a reduction in the rate of nosocomial infections, likely attributable to the shorter duration of mechanical ventilation (104, 105). In the two randomized trials (104, 111) that incorporated infection surveillance, nosocomial infections were frequently (56%) identified in the absence of fever. The combination of GCs and neuromuscular blocking agents significantly increases the risk for prolonged neuromuscular weakness (113). In the ARDS Network trial, although both groups had similar exposure to paralytic agents (49% vs. 42%; *p* = .3), those randomized to methylprednisolone had a higher rate of serious events associated with myopathy or neuropathy (105). The other four trials did not report an increased rate of neuromuscular complications (7, 104, 111, 112).

A reduction in mortality was noted in four studies (7, 104, 111, 112). The ARDS Network trial reported increased 60-day mortality in the subgroup randomized to methylprednisolone after 14 days of ARDS (105). This small subgroup (n = 48), however, had large imbalances in baseline characteristics, and the mortality difference lost significance (*p* = .57) when adjusting for these imbalances (114). The two small clinical trials (n = 68) (7, 111) showed marked reduction in the relative risk of death with GC therapy (2/39 [5%] vs. 11/31 [35%]; relative risk, 0.15; 95% confidence interval, 0.04–0.59; *p* = .007). The three subsequently published larger clinical trials (104, 105, 112), when combined (n = 400), achieved

a distinct reduction in the relative risk of death (82/214 [38%] vs. 152/236 [65%]; relative risk, 0.78; 95% confidence interval, 0.64–0.96; *p* = .02) (114). When analyzing the three trials investigating corticosteroids for durations of >1 wk initiated before day 14 of ARDS (n = 245), mortality was equally decreased (35/144 [24%] vs. 40/101 [40%]; relative risk, 0.62; 95% confidence interval, 0.43–0.90; *p* = .01) (Fig. 5) (114).

The results of one randomized trial (111) indicate that 1 mg·kg⁻¹·day⁻¹ methylprednisolone, given as an infusion and tapered over the course of 4 wks, is associated with a favorable risk-benefit profile when secondary preventive measures are implemented. These measures include 1) intensive infection surveillance, 2) avoidance of paralytic agents, and 3) avoidance of rebound inflammation with premature discontinuation of treatment that may lead to physiologic deterioration and reintubation. It should be noted that the premature and rapid taper of corticosteroids in the ARDS Network trial resulted in a deterioration of the Pao₂/Fio₂ and a higher reintubation rate in the treatment group (105, 114).

Preliminary data suggest that GCs may be of benefit in patients with severe community-acquired pneumonia, liver failure, pancreatitis, patients undergoing cardiopulmonary bypass, and during weaning from mechanical ventilation (7, 10, 11, 75, 96, 115). The potential benefits of treatment with hydrocortisone in these patient subgroups and other critically ill patients deserve further investigation.

How to Treat

Recommendation 8: In patients with septic shock, intravenous hydrocortisone should be given in a dose of 200 mg/day in four divided doses or as a bolus of 100 mg followed by a continuous infusion at 10 mg/hr (240 mg/

day), the optimal initial dosing regimen in patients with early severe ARDS is 1 mg·kg⁻¹·day⁻¹ methylprednisolone as a continuous infusion.

Strength of Recommendation: 1B
 Treat x 7d before taper,

Recommendation 9: The optimal duration of GC treatment in patients with septic shock and early ARDS is unclear. However, based on published studies and pathophysiological data, patients with septic shock should be treated for ≥7 days before tapering, assuming that there is no recurrence of signs of sepsis or shock. Patients with early ARDS should be treated for ≥14 days before tapering.

Strength of Recommendation: 2B

Recommendation 10: GC treatment should be tapered slowly and not stopped abruptly.

Strength of Recommendation: 2B

Recommendation 11: Treatment with fludrocortisone (50 μg orally once daily) is considered optional.

Strength of Recommendation: 2B

Recommendation 12: Dexamethasone is not recommended for the treatment of septic shock or ARDS.

Strength of Recommendation: 1B

Ideally, the dose of GC should be sufficient to down-regulate the proinflammatory response without causing immune-paresis and interfering with wound healing. Similarly, the duration of GC therapy should be guided by the duration of CIRCI and the associated duration of systemic inflammation. The optimal dose and duration of treatment with hydrocortisone/methylprednisolone remains to be determined in well-controlled and well-powered studies. However, the results of published studies do allow us to make a number of recommendations. A number

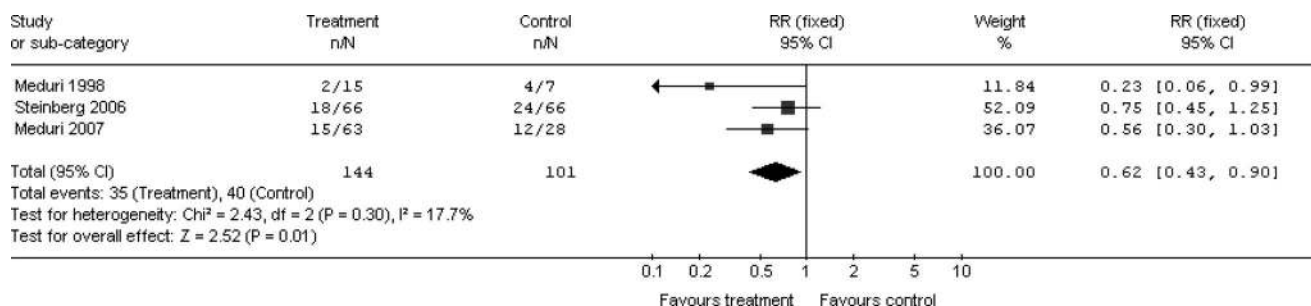


Figure 5. Effects of prolonged glucocorticoid treatment initiated before day 14 of acute lung injury-acute respiratory distress syndrome on survival. Reproduced with permission from Meduri et al (114). RR, relative risk; 95% CI, 95% confidence interval.

of randomized controlled studies have investigated the utility of a high-dose, short-course treatment with corticosteroids in patients with ARDS and sepsis. Doses of methylprednisolone as high as 20–30 mg/kg body weight (10,000 to 40,000 mg of hydrocortisone) during the course of 24 hrs were investigated (116–118). These studies were unable to demonstrate an improved outcome, and there was a higher risk of complications in the patients who received high-dose corticosteroids (116–118). The literature therefore does not support the use of high-dose corticosteroids in critically ill patients (except to prevent/treat rejection in transplant patients).

Myopathy and an increased risk of superinfections are more common in patients receiving >300 mg of hydrocortisone equivalents per day (117, 118). Furthermore, while suppressing an exaggerated proinflammatory response, a dose of 200–300 mg of hydrocortisone per day does not seem to have immunosuppressive effects (119, 120). Based on these data and the treatment protocol used in the French and CORTICUS studies, we recommend that patients with septic shock be treated with 50 mg of hydrocortisone intravenously every 6 hrs or a bolus of 100 mg, followed by a continuous intravenous infusion at 10 mg/hr (340 mg the first day; 240 mg/day on subsequent days). 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 (85, 121–123). Treatment should continue for ≥ 7 days before tapering, assuming that there is no recurrence of signs of sepsis or shock. Hydrocortisone should be tapered slowly and not stopped abruptly. The hydrocortisone dose should be reduced every 2–3 days in small steps, unless there is clinical deterioration, which would then require an increase in hydrocortisone dose. Abruptly stopping hydrocortisone will likely result in a rebound of proinflammatory mediators, with recurrence of the features of shock (and tissue injury) (105, 119). In addition, it should be appreciated that GC treatment itself results in down-regulation of GR levels in most cells, potentiating the rebound phenomenon with the abrupt cessation of GC treatment (70). Currently, the optimal dose and duration of therapy in patients with early severe ARDS is 1 mg·kg⁻¹·day⁻¹ methylpred-

nisolone for ≥ 14 days, followed by a slow taper while monitoring values of oxygenation.

Meduri et al. (124) demonstrated that persistent elevation of inflammatory cytokines predicted a poor outcome in patients with ARDS. Recently, two longitudinal studies in patients with severe community-acquired pneumonia found high levels of circulating inflammatory cytokines 3 wks after clinical resolution of sepsis (125, 126). The larger study, involving 1,886 patients, showed hospital mortality to be associated with higher circulating inflammatory cytokine levels and persistent elevation over time (125). Furthermore, higher circulating interleukin-6 levels at intensive care unit discharge were associated with increased risk of death over 3 months (127). These data support the concept of immune dysregulation in severe sepsis and ARDS (insufficient corticosteroid activity–CIRCI) and suggest that the duration of treatment with GCs should be guided by the duration of elevation of inflammatory cytokines (124). Further studies should explore this concept.

In the French study, patients in the treatment group received hydrocortisone together with fludrocortisone (50 μ g orally once daily), whereas in the CORTICUS study patients received hydrocortisone alone. It is unclear if the addition of fludrocortisone played a role in the favorable outcome of the French study. The benefit of the addition of fludrocortisone in patients with septic shock is currently being investigated in two randomized controlled trials comparing hydrocortisone alone vs. hydrocortisone together with fludrocortisone (www.ClinicalTrials.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 dexamethasone leads to immediate and prolonged suppression of the HPA axis (limiting the value of ACTH testing).

CONCLUSION

CIRCI is a complex and frequent disorder of which our understanding continues to evolve. Although CIRCI may affect a spectrum of critically ill patients, most of the research has focused on patients

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 early severe ARDS (P_{aO_2}/F_{iO_2} of <200) and unresolving ARDS treated with GCs before day 14 suggest that treatment with moderate-dose GCs should be considered in these patients. Tests of adrenal function are not routinely required in these patients. The role of GCs in the management of patients with community-acquired pneumonia, liver failure, pancreatitis, those undergoing cardiac surgery, and other groups of critically ill patients requires further investigation.

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Appendix 1. Modified Grades of Recommendation Assessment, Development, and Evaluation (GRADE) system for Grading the strength of the evidence (15)

Grade of recommendation/ description	Benefits vs. Risk and burdens	Methodological quality of supporting evidence	Implications
1A: Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens or vise versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation can apply to most patients in most circumstances without reservation
1B: Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens or vise versa	RCTs with important limitations or exceptionally strong evidence from observational studies	Strong recommendation can apply to most patients in most circumstances without reservation
1C: Strong recommendation, low quality or very low- quality evidence	Benefits clearly outweigh risk and burdens or vise versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A: Weak recommendation, high quality evidence	Benefits closely balanced with risk and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2B: Weak recommendation, moderate quality evidence	Benefits closely balanced with risk and burden	RCTs with important limitations or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2C: Weak recommendation, low quality or very low quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits risk and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

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