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 μg/dL after adrenocorticotrophic hormone (250 μg) administration or a random total cortisol of <10 μg/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 (Pao_2/Fio_2 of <200 and within 14 days of onset). The adrenocorticotrophic 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 $mg \cdot kg^{-1} \cdot day^{-1}$ 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.

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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 (ESICM). 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 continue until group consensus/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.

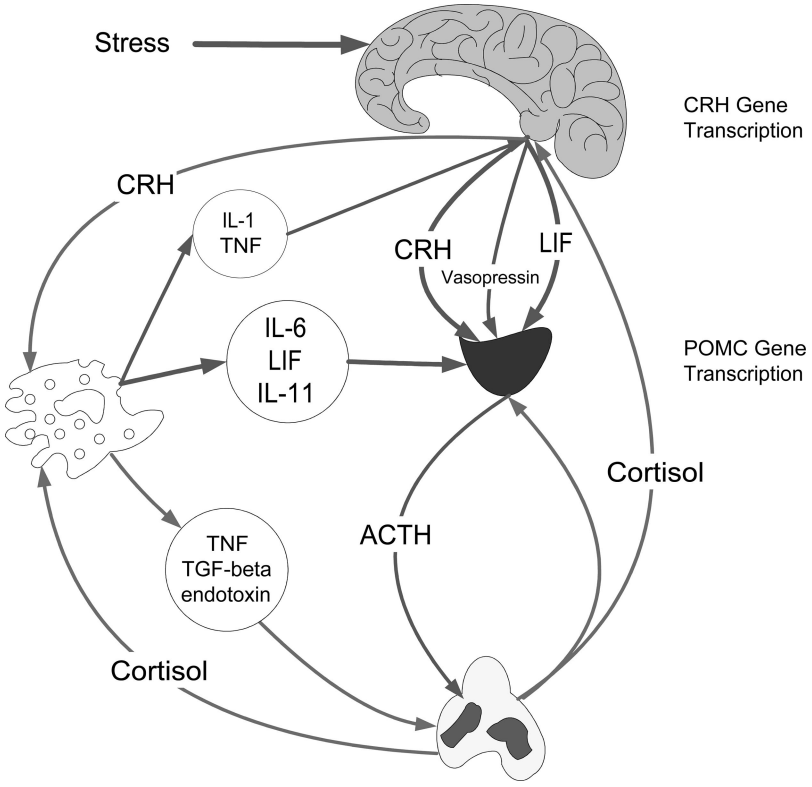

Figure 1. Activation of the hypothalamic-pituitary-adrenal axis by a stressor and the interaction with the inflammatory response. *ACTH*, adrenocorticotrophic hormone; *CRH*, corticotropin-releasing hormone; *IL-6*, interleukin-6; *IL-11*, interleukin-11; *LIF*, leukemia inhibitory factor; *POMC*, proopiomelanocortin; *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%, resulting 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, dehydroepiandrostenedione, 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 κB (NF-κB) 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-κB, which plays a crucial and generalized role in inducing cytokine gene transcription (40–42). NF-κB is normally maintained in an inactive form by sequestration in the cytoplasm through interaction with inhibitory proteins (IκBs). On stimulation by lipopolysaccharide, double-stranded DNA, physical and chemical stresses, and inflammatory cytokines, the latent NF-κB/IκB complex is activated by phosphorylation and proteolytic degradation of IκB, with exposure of the NF-κB nuclear localization sequence. The liberated NF-κB then translocates to the nucleus and binds to promoter regions of target genes to initiate the transcription of multiple cytokines (including 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-κB by increasing the transcription of IκBs and by directly binding to and inhibiting NF-κB (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, systematic 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 μg/dL or a random total cortisol of <10 μg/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 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 μg/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 μg/dL and a random total cortisol of <10 μg/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 mg/dL) and nonresponders (delta cortisol of <9 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

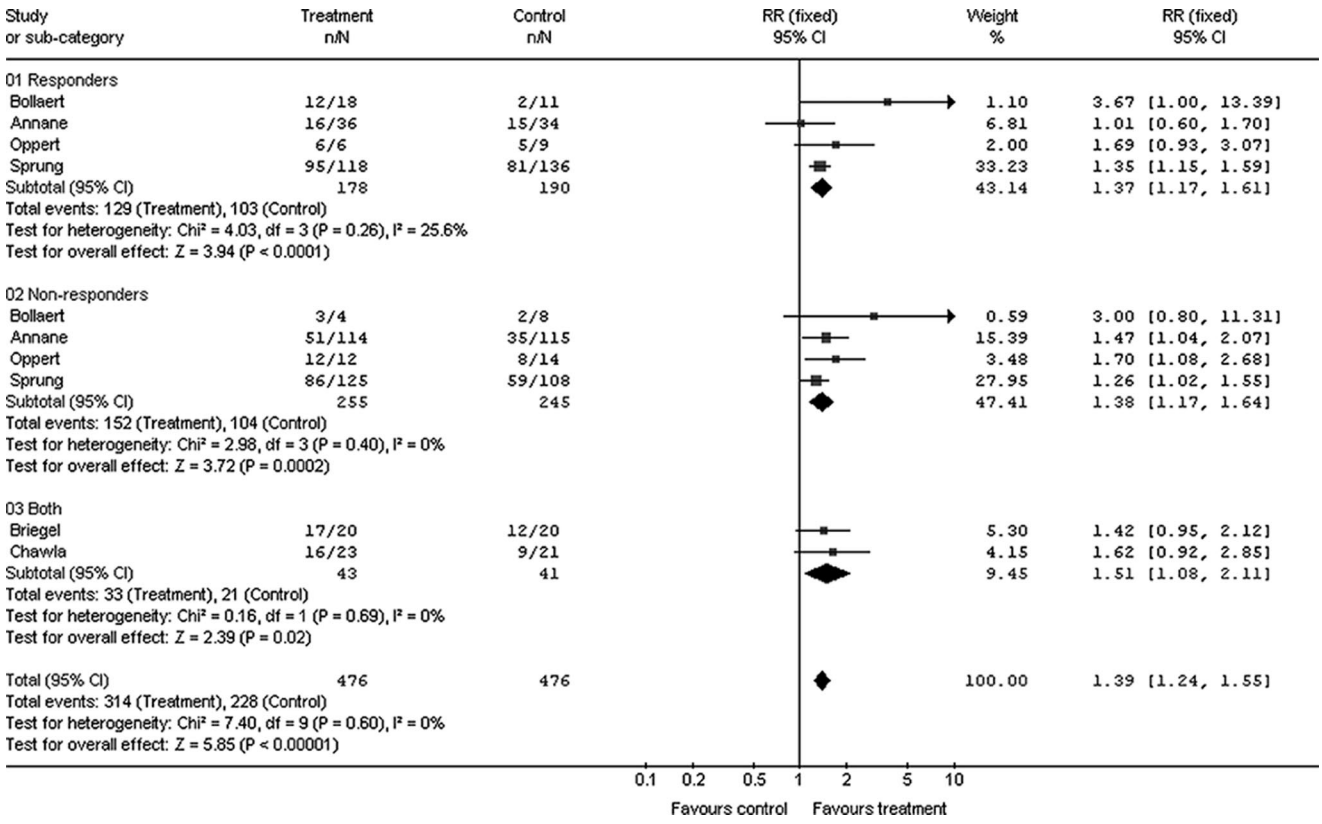

Figure 2. Meta-analysis of treatment with moderate-dose hydrocortisone on shock reversal at day 7 in patients with septic shock grouped by response to adrenocorticotrophic hormone. *RR,* relative risk; *95% CI,* 95% confidence interval.

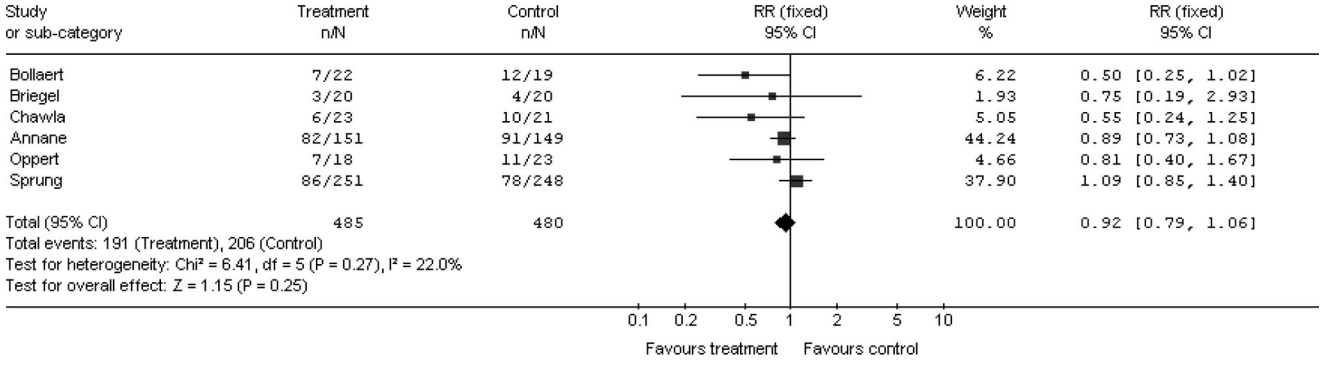

Figure 3. Meta-analysis of treatment with moderate-dose hydrocortisone on 28-day survival in patients with septic shock. *RR,* relative risk; *95% CI,* 95% confidence interval.

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 delay 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 posttraumatic 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 unresolving 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-

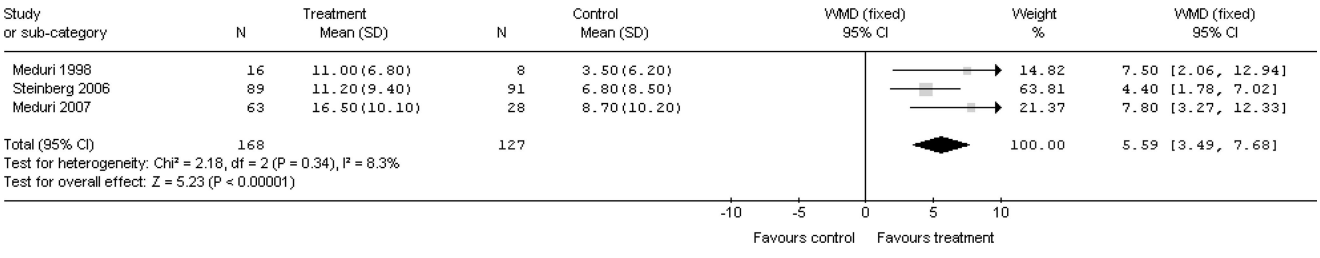

Figure 4. Effects of prolonged methylprednisolone treatment on mechanical ventilation–free days at day 28. Reproduced with permission from Meduri et al (114). *WMD*, weighted mean difference; *95% CI*, 95% confidence interval.

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. 98/186 [52.5%]; 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 $mg \cdot kg^{-1} \cdot day^{-1}$ 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 Pao_2/Fio_2 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 $mg \cdot kg^{-1} \cdot day^{-1}$ methylprednisolone as a continuous infusion.

Strength of Recommendation: 1B

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

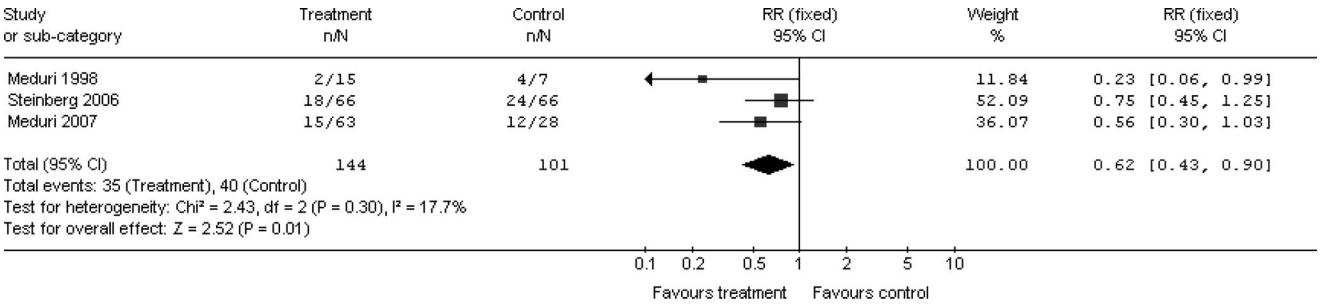

Figure 5. Effects of prolonged glucocorticoid treatment initiated before day 14 of acute lung injury-acute respiratory distress syndrome on survival. Reproduced with permission from Meduri et al (114). *RR*, relative risk; *95% CI*, 95% confidence interval.

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 $mg \cdot kg^{-1} \cdot day^{-1}$ methylprednisolone for ≥14 days, followed by a slow taper while monitoring indices 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 μg 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.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 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 with septic shock and ARDS. At this time, treatment with moderate-dose corticosteroids is recommended in patients with septic shock who have responded poorly to volume resuscitation and vasopressor agents. The consistent positive results reported in patients with early severe ARDS ($Pa_{O_2}/F_{I_{O_2}}$ 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.

REFERENCES

1. Jurney TH, Cockrell JL Jr, Lindberg JS, et al: Spectrum of serum cortisol response to ACTH in ICU patients: Correlation with degree of illness and mortality. *Chest* 1987; 92:292–295
2. Reincke M, Allolio B, Wurth G, et al: The hypothalamic-pituitary-adrenal axis in critical illness: Response to dexamethasone and corticotropin-releasing hormone. *J Clin Endocrinol Metab* 1993; 77:151–156
3. Arlt W, Allolio B: Adrenal insufficiency. *Lancet* 2003; 361:1881–1893
4. Hinshaw LB, Beller BK, Chang AC, et al: Corticosteroid/antibiotic treatment of adrenalectomized dogs challenged with lethal *E. coli*. *Circ Shock* 1985; 16:265–277
5. Darlington DN, Chew G, Ha T, et al: Corticosterone, but not glucose, treatment enables fasted adrenalectomized rats to survive moderate hemorrhage. *Endocrinology* 1990; 127:766–772
6. Marik PE, Zaloga GP: Adrenal Insufficiency in the critically ill: A new look at an old problem. *Chest* 2002; 122:1784–1796
7. Confalonieri M, Urbino R, Potena A, et al: Hydrocortisone infusion for severe community-acquired pneumonia: A preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171:242–248
8. Dimopoulou I, Tsagarakis S: Hypothalamic-pituitary dysfunction in critically ill patients with traumatic and nontraumatic brain injury. *Intensive Care Med* 2005; 31: 1020–1028
9. Tsai MH, Peng YS, Chen YC, et al: Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology* 2006; 43:673–681
10. Eklund A, Leppaniemi A, Kemppainen E, et al: Vasodilatory shock in severe acute pancreatitis without sepsis: Is there any place for hydrocortisone treatment? *Acta Anaesthesiol Scand* 2005; 49:379–384
11. Fernandez J, Escorsell A, Zabalza M, et al:

Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. *Hepatology* 2006; 44:1288–1295
12. Definitions of ACCP evidence-based guidelines, consensus statements, and other reviews and projects. American College of Chest Physicians, 2007. Available at: http://www.chestnet.org/education/guidelines/definitions.php. Accessed February 2, 2008
13. Fink A, Kosecoff J, Chassin M, et al: Consensus methods: Characteristics and guidelines for use. *Am J Public Health* 1984; 74:979–983
14. Williams PL, Webb C, Williams PL, et al: The Delphi technique: A methodological discussion. *J Adv Nurs* 1994; 19:180–186
15. Guyatt G, Gutterman D, Baumann MH, et al: Grading strength of recommendations and quality of evidence in clinical guidelines: Report from an American College of Chest Physicians Task Force. *Chest* 2006; 129:174–181
16. Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655
17. Bernard GR, Artigas A, Brigham KL: The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818–824
18. Cochran W: The combination of estimates from different experiments. *Biometrics* 1954; 10:101–129
19. Berlin JA, Laird NM, Sacks HS, et al: A comparison of statistical methods for combining event rates from clinical trials. *Stat Med* 1989; 8:141–151
20. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21:1539–1558
21. Higgins JP, Thompson SG, Deeks JJ, et al: Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557–560
22. Chrousos GP: The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995; 332:1351–1362
23. Carrasco GA, Van de Kar LD, Carrasco GA, et al: Neuroendocrine pharmacology of stress. *Eur J Pharmacol* 2003; 463:235–272
24. Miller DB, O'Callaghan JP, Miller DB, et al: Neuroendocrine aspects of the response to stress. *Metab Clin Exp* 2002; 51:5–10
25. Dunn JF, Nisula BC, Rodbard D: Transport of steroid hormones: Binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. *J Clin Endocrinol Metab* 1981; 53:58–68
26. Mueller UW, Potter JM: Binding of cortisol to human albumin and serum: The effect of protein concentration. *Biochem Pharmacol* 1981; 30:727–733
27. Ho JT, Al-Musalhi H, Chapman MJ, et al: Septic shock and sepsis: A comparison of total and free plasma cortisol levels. *J Clin Endocrinol Metab* 2006; 91:105–114
28. Dimopoulou I, Alevizopoulou P, Dafni U, et al: Pituitary-adrenal response to human corticotropin-releasing hormone in critically ill patients. *Intensive Care Med* 2007; 33:454–459
29. Arlt W, Stewart PM: Adrenal corticosteroid biosynthesis, metabolism, and action. *Endocrinol Metab Clin North Am* 2005; 34: 293–313
30. Borkowski AJ, Levin S, Delcroix C, et al: Blood cholesterol and hydrocortisone production in man: Quantitative aspects of the utilization of circulating cholesterol by the adrenals at rest and under adrenocorticotropin stimulation. *J Clin Invest* 1967; 46: 797–811
31. Yaguchi H, Tsutsumi K, Shimono K, et al: Involvement of high density lipoprotein as substrate cholesterol for steroidogenesis by bovine adrenal fasciculo-reticularis cells. *Life Sci* 1998; 62:1387–1395
32. Acton S, Rigotti A, Landschultz KT, et al: Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. *Science* 1996; 271:518–520
33. Calco D, Gomez-Coronado D, Lasuncion MA, et al: CLA-I is an 85-kD plasma membrane glycoprotein that acts as a high affinity receptor for both native (HDL, LDL, and VLDL) and modified (OxLDL and AcLDL) lipoproteins. *Arterioscler Thromb Vasc Biol* 1997; 17:2341–2349
34. de la Llera-Moya M, Connelly MA, Drazul D, et al: Scavenger receptor class B type 1 affects cholesterol homeostasis by magnifying cholesterol flux between cells and HDL. *J Lipid Res* 2001; 42:1969–1978
35. Liu J, Heikkila P, Meng QH, et al: Expression of low and high density lipoprotein receptor genes in human adrenals. *Eur J Endocrinol* 2000; 142:677–682
36. Rhen T, Cidlowski JA: Antiinflammatory action of glucocorticoids–new mechanisms for old drugs. *N Engl J Med* 2005; 353: 1711–1723
37. Sinars CR, Cheung-Flynn J, Rimerman RA, et al: Structure of the large FK506-binding protein FKBP51, an Hsp90-binding protein and a component of steroid receptor complexes. *Proc Nat Acad Sci U S A* 2003; 100: 868–873
38. Vermeer H, Hendriks-Stegeman BI, van der BB, et al: Glucocorticoid-induced increase in lymphocytic FKBP51 messenger ribonucleic acid expression: A potential marker for glucocorticoid sensitivity, potency, and bioavailability. *J Clin Endocrinol Metab* 2003; 88:277–284
39. Galon J, Franchimont D, Hiroi N, et al: Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells. *FASEB J* 2002; 16:61–71
40. Auphan N, Didonato JA, Rosette C, et al: Immunosuppression by glucocorticoids: Inhibition of NF-kappa B activity through induction of I kappa B synthesis. *Science* 1995; 270:286–290
41. Barnes PJ, Adcock I: Anti-inflammatory actions of steroids: Molecular mechanisms. *Trends Pharmacol Sci* 1993; 14:436–441
42. Barnes PJ, Karin M: Nuclear factor-kB-A pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med* 1997; 336:1066–1071
43. Oelkers W: Adrenal insufficiency. *N Engl J Med* 1996; 335:1206–1212
44. Collins S, Caron MG, Lefkowitz RJ: Beta-adrenergic receptors in hamster smooth muscle cells are transcriptionally regulated by glucocorticoids. *J Biol Chem* 1988; 263: 9067–9070
45. Sakaue M, Hoffman BB: Glucocorticoids induce transcription and expression of the alpha 1B adrenergic receptor gene in DTT1 MF-2 smooth muscle cells. *J Clin Invest* 1991; 88:385–389
46. Limbourg FP, Huang Z, Plumier JC, et al: Rapid nontranscriptional activation of endothelial nitric oxide synthase mediates increased cerebral blood flow and stroke protection by corticosteroids. *J Clin Invest* 2002; 110:1729–1738
47. Hafezi-Moghadam A, Simoncini T, Yang Z, et al: Acute cardiovascular protective effects of corticosteroids are mediated by nontranscriptional activation of endothelial nitric oxide synthase. *Nat Med* 2002; 8:473–479
48. Bobadilla NA, Tapia E, Jimenez F, et al: Dexamethasone increases eNOS gene expression and prevents renal vasoconstriction induced by cyclosporin. *Am J Physiol* 1999; 277:F464–F471
49. Murata T, Hori M, Sakamoto K, et al: Dexamethasone blocks hypoxia-induced endothelial dysfunction in organ-cultured pulmonary arteries. *Am J Respir Crit Care Med* 2004; 170:647–655
50. Cooper MD, Stewart PM: Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; 348:727–734
51. Widmer IE, Puder JJ, Konig C, et al: Cortisol response in relation to the severity of stress and illness. *J Clin Endocrinol Metab* 2005; 90:4579–4586
52. Vogeser M, Groetzner J, Kupper C, et al: Free serum cortisol during the postoperative acute phase response determined by equilibrium dialysis liquid chromatography-tandem mass spectrometry. *Clin Chem Lab Med* 2003; 41:146–151
53. Annane D, Maxime V, Ibrahim F, et al: Diagnosis of adrenal insufficiency in severe sepsis and septic shock. *Am J Respir Crit Care Med* 2006; 174:1319–1326
54. Vella A, Nippoldt TB, Morris JC III: Adrenal hemorrhage: A 25-year experience at the Mayo Clinic. *Mayo Clin Proc* 2001; 76: 161–168
55. Kovacs KA, Lam YM, Pater JL: Bilateral massive adrenal hemorrhage: Assessment of

putative risk factors by the case-control method. *Medicine* 2001; 80:45–53
56. Deeb SA, Rosenberg RB, Wilkerson RJ, et al: Adrenal hemorrhage in a pediatric burn patient. *Burns* 2001; 27:658–661
57. Weyrich P, Balletshofer B, Hoeft S, et al: Acute adrenocortical insufficiency due to heparin-induced thrombocytopenia with subsequent bilateral haemorrhagic infarction of the adrenal glands. *Vasa* 2001; 30: 285–288
58. Espinosa G, Santos E, Cervera R, et al: Adrenal involvement in the antiphospholipid syndrome: Clinical and immunologic characteristics of 86 patients. *Medicine* 2003; 82:106–118
59. Arnason JA, Graziano FM: Adrenal insufficiency in the antiphospholipid antibody syndrome. *Semin Arthritis Rheum* 1995; 25:109–116
60. Briegel J, Scheelling G, Haller M, et al: A comparison of the adrenocortical response during septic shock and after complete recovery. *Intensive Care Med* 1996; 22: 894–899
61. Meduri GU, Yates CR: Systemic inflammation-associated glucocorticoid resistance and outcome of ARDS. *Ann N Y Acad Sci* 2004; 1024:24–53
62. Ito K, Ito M, Elliott WM, et al: Decreased histone deacetylase activity in chronic obstructive pulmonary disease. *N Engl J Med* 2005; 352:1967–1976
63. Hew M, Bhavsar P, Torrego A, et al: Relative corticosteroid insensitivity of peripheral blood mononuclear cells in severe asthma. *Am J Respir Crit Care Med* 2006; 174: 134–141
64. Chikanza IC, Kozaci DL: Corticosteroid resistance in rheumatoid arthritis: Molecular and cellular perspectives. *Rheumatology* 2004; 43:1337–1345
65. Chikanza IC, Kozaci D, Chernajovsky Y: The molecular and cellular basis of corticosteroid resistance. *J Endocrinol* 2003; 179: 301–310
66. Pariante CM, Pearce BD, Pisell TL, et al: The proinflammatory cytokine, interleukin-1alpha, reduces glucocorticoid receptor translocation and function. *Endocrinology* 1999; 140:4359–4366
67. Liu LY, Sun B, Tian Y, et al: Changes of pulmonary glucocorticoid receptor and phospholipase A2 in sheep with acute lung injury after high dose endotoxin infusion. *Am Rev Respir Dis* 1993; 148:878–881
68. Kino T, Ichijo T, Chrousos GP: FLASH interacts with p160 coactivator subtypes and differentially suppresses transcriptional activity of steroid hormone receptors. *J Steroid Biochem Mol Biol* 2004; 92:357–363
69. Meduri GU, Muthiah MP, Carratu P, et al: Nuclear factor-kappaB- and glucocorticoid receptor alpha–mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome: Evidence for inflammation-induced target tissue resistance to glucocorticoids. *Neuroimmunomodulation* 2005; 12:321–338
70. Schaaf MJ, Cidlowski JA: Molecular mechanisms of glucocorticoid action and resistance. *J Steroid Biochem Mol Biol* 2002; 83:37–48
71. Creed TJ, Probert CS: Review article: Steroid resistance in inflammatory bowel disease. Mechanisms and therapeutic strategies. *Aliment Pharmacol Ther* 2007; 25: 111–122
72. Lewis-Tuffin LJ, Cidlowski JA: The physiology of human glucocorticoid receptor beta (hGRbeta) and glucocorticoid resistance. *Ann N Y Acad Sci* 2006; 1069:1–9
73. Xu D, Buehner A, Xu J, et al: A polymorphic glucocorticoid receptor in a mouse population may explain inherited altered stress response and increased anxiety-type behaviors. *FASEB J* 2006; 20:2414–2416
74. De Iudicibus S, Stocco G, Martelossi S, et al: Association of BclI polymorphism of the glucocorticoid receptor gene locus with response to glucocorticoids in inflammatory bowel disease. *Gut* 2007; 56:1319–1320
75. Marik PE, Gayowski T, Starzl TE, et al: The hepatoadrenal syndrome: A common yet unrecognized clinical condition. *Crit Care Med* 2005; 33:1254–1259
76. Murphy JF, Purdue GF, Hunt JL: Acute adrenal insufficiency in the patient with burns. *J Burn Care Rehabil* 1993; 14: 155–157
77. Winter W, Kamolz L, Donner A, et al: Hydrocortisone improved haemodynamics and fluid requirement in surviving but not nonsurviving of severely burned patients. *Burns* 2003; 29:717–720
78. De Waele JJ, Hoste EA, Baert D, et al: Relative adrenal insufficiency in patients with severe acute pancreatitis. *Intensive Care Med* 2007; 33:1754–1760
79. Gloor B, Uhl W, Tcholakov O, et al: Hydrocortisone treatment of early SIRS in acute experimental pancreatitis. *Dig Dis Sci* 2001; 46:2154–2161
80. Meyer NJ, Hall JB: Relative adrenal insufficiency in the ICU: Can we at least make the diagnosis? *Am J Respir Crit Care Med* 2006; 174:1282–1283
81. Marik PE: The adrenal exhaustion syndrome in patients with liver disease. *Intensive Care Med* 2006; 32:275–280
82. Van der Voort PHJ, Koopman M: Follow up corticotropin stimulating tests during ICU stay. *Intensive Care Med* 2004; 30(Suppl 1):S61
83. Beishuizen A, Vermes I, Hylkema BS, et al: Relative eosinophilia and functional adrenal insufficiency in critically ill patients. Letter. *Lancet* 1999; 353:1675–1676
84. Annane D, Sebille V, Troche G, et al: A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA* 2000; 283: 1038–1045
85. Arafah BM: Hypothalamic-pituitary adrenal function during critical illness: Limitations of current assessment methods. *J Clin Endocrinol Metab* 2006; 91:3725–3745
86. le Roux CW, Chapman GA, Kong WM, et al: Free cortisol index is better than serum total cortisol in determining hypothalamic-pituitary-adrenal status in patients undergoing surgery. *J Clin Endocrinol Metab* 2003; 88:2045–2048
87. Hamrahian AH, Oseni TS, Arafah BM: Measurement of serum free cortisol in critically ill patients. *N Engl J Med* 2004; 350: 1629–1638
88. Vogeser M, Briegel J, Zachoval R: Dialyzable free cortisol after stimulation with Synacthen. *Clin Biochem* 2002; 35:539–543
89. Salgado DR, Verdeal JC, Rocco JR: Adrenal function testing in patients with septic shock. *Crit Care* 2006; 10:R149
90. Vogeser M, Mohnle P, Briegel J: Free serum cortisol: Quantification applying equilibrium dialysis or ultrafiltration and an automated immunoassay system. *Clin Chem Lab Med* 2007; 45:521–525
91. Vogeser M, Briegel J, Jacob K: Determination of serum cortisol by isotope-dilution liquid-chromatography electrospray ionization tandem mass spectrometry with online extraction. *Clin Chem Lab Med* 2001; 39: 944–947
92. Cohen J, Ward G, Prins J, et al: Variability of cortisol assays can confound the diagnosis of adrenal insufficiency in the critically ill population. *Intensive Care Med* 2006; 32: 1901–1905
93. Rothwell PM, Udwadia ZF, Lawler PG: Cortisol response to corticotropin and survival in septic shock. *Lancet* 1991; 337:582–583
94. Bollaert PE, Fieux F, Charpentier C, et al: Baseline cortisol levels, cortisol response to corticotropin, and prognosis in late septic shock. *Shock* 2003; 19:13–15
95. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871
96. Huang CJ, Lin HC: Association between adrenal insufficiency and ventilator weaning. *Am J Respir Crit Care Med* 2006; 173: 276–280
97. Loisa P, Uusaro A, Ruokonen E: A single adrenocorticotropic hormone stimulation test does not reveal adrenal insufficiency in septic shock. *Anesth Analg* 2005; 101: 1792–1798
98. Bouachour G, Roy PM, Guiraud MP, et al: The repetitive short corticotropin stimulation test in patients with septic shock. *Ann Intern Med* 1995; 123:962–963
99. Marik PE, Zaloga GP: Adrenal insufficiency during septic shock. *Crit Care Med* 2003; 31:141–145
100. Chawla K, Kupfer Y, Tessler S: Hydrocortisone reverses refractory septic shock. *Crit Care Med* 1999; 27(Suppl):A33
101. Oppert M, Schindler R, Husuang C, et al: Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early

hyperdynamic septic shock. *Crit Care Med* 2005; 33:2457–2464
102. Bollaert PE, Charpentier C, Levy B, et al: Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998; 26:645–650
103. Briegel J, Forst H, Haller M, et al: Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; 27:723–732
104. Meduri GU, Golden E, Freire AX, et al: Methylprednisolone infusion in patients with early severe ARDS: Results of a randomized trial. *Chest* 2007; 131:954–963
105. The Acute Respiratory Distress Syndrome Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354: 1671–1684
106. Sprung CL, Annane D, Keh D, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124
107. Annane D, Briegel J, Keh D, et al: Clinical equipoise remains for issues of adrenocorticotropic hormone administration, cortisol testing, and therapeutic use of hydrocortisone. *Crit Care Med* 2003; 31:2250–2251
108. Annane D, Vignon P, Renault A, et al: Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: A randomised trial. *Lancet* 2007; 370:676–684
109. Russell JA, Walley KR, Singer J, et al: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887
110. Schelling G, Stoll C, Kapfhammer HP, et al: The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder and health-related quality of life in survivors. *Crit Care Med* 1999; 27: 2678–2683
111. Meduri GU, Headley S, Golden E, et al: Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 1998; 280:159–165
112. Annane D, Sebille V, Bellissant E: Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. *Crit Care Med* 2006; 34:22–30
113. Leatherman JW, Fluegle WL, David WS, et al: Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med* 1996; 153:1686–1690
114. Meduri GU, Marik PE, Chrousos GP, et al: Steroid treatment in ARDS: A critical appraisal of the ARDS network trial and the recent literature. *Intensive Care Med* 2008; 34:61–69
115. Halonen J, Halonen P, Jarvinen O, et al: Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: A randomized controlled trial. *JAMA* 2007; 14: 1562–1567
116. Keh D, Sprung CL: Use of corticosteroid therapy in patients with sepsis and septic shock: An evidence-based review. *Crit Care Med* 2004; 32:S527–S533
117. Annane D, Bellissant E, Bollaert PE, et al: Corticosteroids for severe sepsis and septic shock: A systematic review and meta-analysis. *BMJ* 2004; 329:480–489
118. Minneci PC, Deans KJ, Banks SM, et al: Meta-analysis: The effect of steroids on survival and shock during sepsis depends on the dose. *Ann Intern Med* 2004; 141:47–56
119. Keh D, Boehnke T, Weber-Cartens S, et al: Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: A double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003; 167:512–520
120. Kaufmann I, Briegel J, Schliephake F, et al: Stress doses of hydrocortisone in septic shock: Beneficial effects on opsonization-dependent neutrophil functions. *Intensive Care Med* 2008; 34:344–349
121. Loisa P, Parviainen I, Tenhunen J, et al: Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: A prospective randomized trial. *Crit Care* 2007; 11:R21
122. Weber-Carstens S, Deja M, Bercker S, et al: Impact of bolus application of low-dose hydrocortisone on glycemic control in septic shock patients. *Intensive Care Med* 2007; 33:730–733
123. Egi M, Bellomo R, Stachowski E, et al: Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006; 105:244–252
124. Meduri GU, Headley S, Kohler G, et al: Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS: Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. *Chest* 1995; 107:1062–1073
125. Kellum JA, Kong L, Fink MP, et al: Understanding the inflammatory cytokine response in pneumonia and sepsis: Results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Arch Intern Med* 2007; 167:1655–1663
126. Lekkou A, Karakantza M, Mouzaki A, et al: Cytokine production and monocyte HLA-DR expression as predictors of outcome for patients with community-acquired severe infections. *Clin Diagn Lab Immunol* 2004; 11:161–167
127. Yende S, Knong L, Weussfeld J: Inflammatory markers prior to hospital discharge predict subsequent mortality after community acquired pneumonia: Proceedings of the American Thoracic Society. *Am J Respir Crit Care Med* 2006; 3:A836

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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