Critical Illness-Related Corticosteroid Insufficiency (CIRCI): A Narrative Review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM)

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Dr. Annane has been involved with research relating to this guideline. Dr. Pastores participates in the American College of Physicians: Speaker at ACP Critical Care Update Precourse, the American College of Chest Physicians (CHEST) (faculty speaker at Annual Congress), the American Thoracic Society (ATS): Moderator at Annual Meeting, the European Society of Intensive Care Medicine (EISCM) (co-chair of Corticosteroid Guideline in collaboration with SCCM), and the Korean Society of Critical Care Medicine (co-director and speaker at Multiprofessional Critical Care Board Review Course). He has spoken on the topic of corticosteroid use in critical illness and specifically in sepsis at the International Symposium in Critical and Emergency Medicine in March 2017. Dr. Arlt participates in the Society for Endocrinology UK (Chair of the Clinical Committee, member of Council, member of the Nominations Committee) and the Endocrine Society USA (member, Publication Core Committee). Dr. Briegel participates in the European Society of Intensive Care Medicine, the Deutsche interdisziplinäre Vereinigung Intensivmedizin, and the Deutsche Gesellschaft für Anästhesie und Intensivmedizin, and he has given lectures and talks on hydrocortisone treatment of septic shock. Dr. Cooper participates in a range of specialist societies relating to endocrinology and bone disease. Dr. Meduri disclosed he is a government employee. Dr. Olsen participates in the American College of Clinical Pharmacy (grant review committee), and he represents the American Society of Health-System Pharmacists on the National Quality Forum for Surgery Measures. Dr. Rochwerg disclosed he is a methodologist for ATS, CBS, ESCIM, ASH. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Objective: To provide a narrative review of the latest concepts and understanding of the pathophysiology of critical illness-related corticosteroid insufficiency (CIRCI).

Participants: A multi-specialty task force of international experts in critical care medicine and endocrinology and members of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.

Data Sources: Medline, Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews.

Results: Three major pathophysiologic events were considered to constitute CIRCI: dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, altered cortisol metabolism, and tissue resistance to glucocorticoids. The dysregulation of the HPA axis is complex, involving multidirectional crosstalk between the CRH/ACTH pathways, autonomic nervous system, vasopressinergic system, and immune system. Recent studies have demonstrated that plasma clearance of cortisol is markedly reduced during critical illness, explained by suppressed expression and activity of the primary cortisol-metabolizing enzymes in the liver and kidney. Despite the elevated cortisol levels during critical illness, tissue resistance to glucocorticoids is believed to occur due to insufficient glucocorticoid alpha-mediated anti-inflammatory activity.

Conclusions: Novel insights into the pathophysiology of CIRCI add to the limitations of the current diagnostic tools to identify at-risk patients and may also impact how corticosteroids are used in patients with CIRCI. (*Crit Care Med* 2017; XX:00–00)

Key Words: Corticosteroid insufficiency; critical illness; sepsis; glucocorticoids; glucocorticoid receptor

INTRODUCTION

In 2008 an international multidisciplinary task force convened by the Society of Critical Care Medicine (SCCM) coined the term *critical illness-related corticosteroid insufficiency* (CIRCI) to describe impairment of the hypothalamic–pituitary–adrenal (HPA) axis during critical illness (1). CIRCI was defined as inadequate cellular corticosteroid activity for the severity of the patient's critical illness, manifested by insufficient glucocorticoid–glucocorticoid receptor-mediated down regulation of pro-inflammatory transcription factors. CIRCI is thought to occur in several acute conditions including sepsis and septic shock, severe community-acquired pneumonia, acute respiratory distress syndrome (ARDS), cardiac arrest, head injury, trauma, burns, and post-major surgery. This narrative review, performed by a multi-specialty task force of international experts and members of the SCCM and the European Society of Intensive Care Medicine (ESICM), focuses on the latest concepts and understanding of the pathophysiology of CIRCI during critical illness.

Hypotalamic Pituitary Adrenal Axis and the Physiological Response to Stress

Systemic inflammation–a central component of the innate immune system–is a highly organized response to infectious and non-infectious threats to homeostasis that consists of at least three major domains (1): the stress system mediated by the HPA axis and the locus ceruleus-norepinephrine/sympathetic nervous system (2), the acute-phase reaction (3), and the target (vital organs) tissue defense response (2, 3). Whereas appropriately regulated inflammation–tailored to stimulus and time (4)–is beneficial, excessive or persistent systemic inflammation incites tissue destruction and disease progression (5).

Overwhelming systemic inflammation that characterizes critical illness is partly driven by an imbalance between hyperactivated inflammatory pathways such as the classical nuclear factor-kappa B (NF-kB) signaling system (6) and the less activated or dysregulated HPA-axis response (7). The activated glucocorticoid-glucocorticoid receptor-alpha (GC-GRα) complex plays a fundamental role in the maintenance of both resting and stress-related homeostasis and influences the physiologic adaptive reaction of the organism against stressors (2). The activated GC-GRα complex exerts its activity at the cytoplasmic level and on nuclear deoxyribonucleic acid (nDNA) and mitochondrial DNA (mtDNA) (8) affecting thousands of genes involved in response to stress and non-stress states (9). Individual genetic variants of the glucocorticoid receptor may also affect both the basic cellular phenotypes, i.e., GR expression levels and the overall HPA axis stress response through either an altered GC response or sensitivity (10).

Cortisol Synthesis

The adrenal glands produce glucocorticoids (cortisol), mineralocorticoids (aldosterone), and adrenal androgens (dehydroepiandrosterone, DHEA) using cholesterol as a substrate, and upon stimulation by adrenocorticotropic hormone (ACTH), also known as corticotropin (**Figure 1**). ACTH is a short half-life, fast-acting 39-amino acid peptide produced from the cleavage of a large precursor, pro-opiomelanocortin. ACTH stimulatory activity is regulated by corticotropin releasing hormone (CRH) and to a lesser extent by arginine vasopressin (AVP), both acting synergistically. Steroidogenic cholesterol is stored in lipid droplets as cholesteryl esters. Adrenal mitochondria play a critical role in adrenocortical cell steroidogenesis, converting intracellular cholesterol to cortisol. The final steps in glucocorticoid biosynthesis are catalyzed by two closely related mitochondrial P450-type enzymes: CYP11B1 and CYP11B2 (11). Cortisol is the major endogenous glucocorticoid secreted by the human adrenal cortex. Cortisol is released in a circadian rhythm: cortisol production is at its peak in the early hours of the morning and then secretion gradually declines over the course of the day.

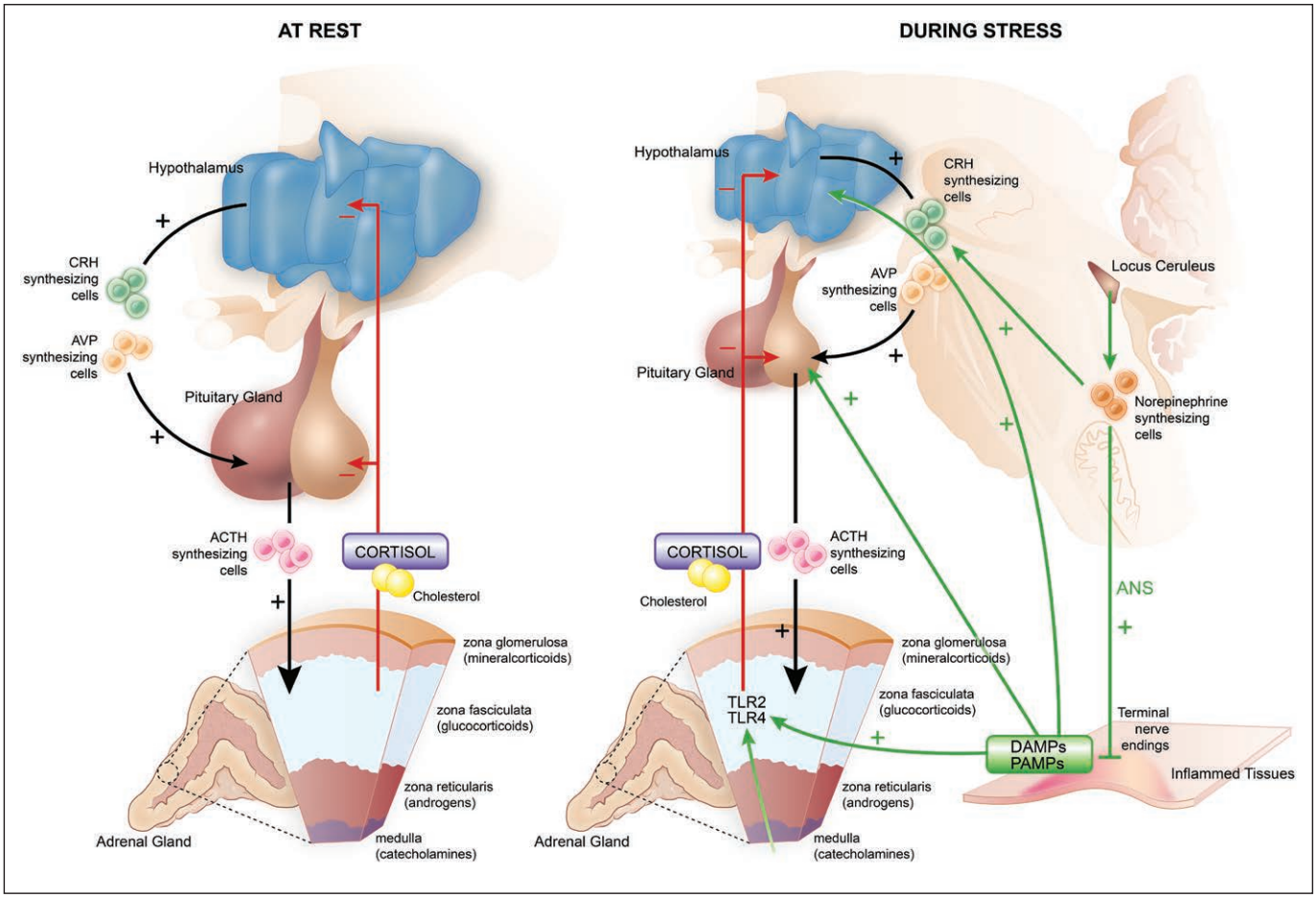

Figure 1. Glucocorticoid synthesis at rest and during stress. At rest, glucocorticoids (e.g., cortisol) are produced from the zona fasciculata of the adrenal cortex upon stimulation by adrenocorticotropic hormone (ACTH) released in the blood from the anterior pituitary gland. Both corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), synthesized in the hypothalamus, contribute to the synthesis and release of ACTH by pituitary cells. During stress, the synthesis of ACTH is additionally stimulated by norepinephrine, mainly produced in the locus ceruleus. At the level of inflamed tissues, terminal nerve endings of afferent fibers of the autonomic nervous system (ANS) have receptors for damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) allowing them to sense the threat and activate the noradrenergic/CRH system. These DAMPs and PAMPs can also directly stimulate adrenal cortex cells that possess Toll-like receptors (TLR), resulting in ACTH-independent cortisol synthesis. In addition, paracrine routes allow the medulla to also stimulate glucocorticoid synthesis independently of ACTH.

Cortisol itself exerts inhibitory control on the pituitary and hypothalamus to regulate its release. The estimated daily production rate of cortisol is 27–37.5 μmol/day (5–7 mg/m^2/day) (12). There is limited adrenal storage of cortisol. Under the stress of critical illness, the regulation of cortisol production becomes much more complex involving multidirectional crosstalk between the CRH/ACTH pathways, autonomic nervous system, vasopressinergic system, and immune system (Figure 1). Acute stress induces rapid release of ACTH via CRH and AVP and loss of the circadian rhythm of cortisol secretion. In critically ill patients, increased cortisol levels do not appear to be due to increased adrenocortical sensitivity to ACTH (13). The dissociation of cortisol from ACTH could be due to direct production of cortisol from the adrenal glands or to reduced metabolism of cortisol and thus an increased systemic half-life. Cortisol production rates in critically ill patients were recently shown to be either unaltered or only slightly increased compared with matched control subjects tested in an ICU environment (14, 15).

Cortisol Transport and Metabolism

In plasma, a large proportion (80%–90%) of circulating cortisol is bound with high affinity to corticosteroid-binding globulin (CBG), with smaller (10%–15%) proportions bound with low affinity to albumin or present in the 'free' unbound form. The binding capacity of CBG is typically saturated at cortisol concentrations of 22–25 μg/dL. When cortisol levels are higher than 25 μg/dL, there is an increased proportion of albumin-bound and free cortisol, whereas the amount of CBG-bound cortisol remains the same. Albumin and CBG are negative acute phase reactants and rapidly decrease in critical illness in proportion to the severity of illness (16). In septic patients, reduction in CBG levels correlates with plasma interleukin-6 (IL-6) levels (17).

Cortisol is metabolized primarily in the liver and the kidneys. In the liver, the most important enzymes catalyzing the initial steps in cortisol metabolism are the 5 α/β-reductases, whereas in the kidney, cortisol is broken down to the inactive metabolite cortisone by the 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2 enzyme (14). Some cortisol can

be regenerated from cortisone in extra-adrenal tissues (liver, adipose tissue, skeletal muscles) through the activity of the 11β-HSD1 enzyme. The adverse metabolic complications associated with corticosteroid excess involve the key metabolic tissues (liver, adipose tissue, and skeletal muscle) which have comparatively high 11β-HSD1 activity.

In stressed conditions, the increase in cortisol level can lead to an increase in the free fraction in the circulation. Additionally, plasma CBG levels can decrease through reduced liver synthesis and increased peripheral cleavage by activated neutrophil elastases. These effects act to increase the amount of cortisol delivered to the tissues. During stress the metabolism of cortisol can also undergo significant changes. The expression and activity of 5-reductases within the liver and probably other tissues is decreased in response to inflammation (14). Renal 11β-HSD2 is also decreased in response to inflammation, while the expression of 11β-HSD1 is increased in some tissues (18). Up regulation of 11β-HSD1 activity is modulated by inflammatory cytokines (tumor necrosis factor-alpha [TNF-α], IL-1β). These effects would be expected to increase the cortisol action at the level of specific tissues and also increase the half-life of circulating cortisol (18, 19).

Cellular Cortisol Signaling

Cortisol is a lipophilic hormone that enters cells passively and binds to specific cytoplasmic receptors, or to membrane sites. There are two types of glucocorticoid receptors (GR). The type 1 receptor is more commonly referred to as the mineralocorticoid receptor (MR) and the type 2 receptor as the classical GR. Both the GR and the MR can bind aldosterone and cortisol. In many tissues the ability of the MR to bind cortisol is reduced by the expression of the 11β-HSD2 enzyme and the conversion to inactive cortisone. The MR has a higher affinity for cortisol and aldosterone than the GR and is thought to be important for signaling at low corticosteroid concentrations. Although the MR is involved in some inflammatory responses, the classic GR is thought to be more important in mediating the glucocorticoid responses to stress and inflammation. Several transcriptional and translational isoforms of the GR exist, which appear to vary in their tissue distribution and gene-specific effects. Our current understanding of the GR's mechanism of action is mainly obtained from research on the almost ubiquitous and most abundant full-length GRα isoform (20).

In the absence of glucocorticoids, the GR is primarily present in the cytoplasm as part of a multiprotein complex with chaperone proteins, heat shock proteins, and immunophilins (FKBP51 and FKBP52). Upon binding of glucocorticoid, the GR undergoes a conformational change, dissociates from the chaperone proteins, and enters the nucleus and mitochondria, where it binds to positive (transactivation) or negative (cis-repression) specific DNA regions termed glucocorticoid responsive elements (GRE) to regulate transcription and translation of target genes in a cell- and gene-specific manner (21, 22) (**Figure 2**). The glucocorticoid receptor can inhibit the expression of pro-inflammatory genes independently of DNA binding by physically interacting (via tethering) with the transcription factor p65, a subunit of nuclear factor κB, an effect referred to as transrepression. This interaction inhibits p65–p50 heterodimer translocation into and action at the nucleus (21). Alternatively, in transactivation, GR binding to GRE in the promoter regions of target genes is followed by recruitment of other proteins such as co-activators, resulting in increased pro-inflammatory gene transcription.

Glucocorticoids can induce some anti-inflammatory effects through non-genomic effects (Figure 2). Specifically, membrane-bound GR can activate kinase pathways within minutes. The activation of the mitogen-activated protein kinase (MAPK) pathway results in the inhibition of cytosolic phospholipase A2α, whereas activated phosphatidylinositol 3-kinase leads to the induction of endothelial nitric oxide synthetase (eNOS) and the subsequent production of nitric oxide (21). Endothelial GR is a critical regulator of NO synthesis in sepsis (23). In experimental lipopolysaccharide (LPS) models, tissue-specific deletion of the endothelial GR results in prolonged activation of NF-kB with increased expression of eNOS and inducible nitric oxide synthase (iNOS), TNF-α, and IL-6 (23). Importantly, the presence of endothelial GR is required for dexamethasone to rescue the animals from lipopolysaccharide (LPS)-induced morbidity and mortality (24). Glucocorticoids may also impair T-cell receptor signaling through non-genomic inhibition of FYN oncogene-related kinase and lymphocyte-specific protein tyrosine kinase by the glucocorticoid receptor (21).

In addition to the wild-type glucocorticoid receptor GRα, two splice variants involving the hormone-binding domain exist, namely GRβ and GR-P (also known as GRδ) (25, 26). GRβ differs from the GRα at the C terminus, resulting in a lack of binding to GCs, constitutive localization in the nucleus, and an inability to transactivate a GC-responsive reporter gene. However, it acts as a dominant-negative inhibitor of GRα genomic transactivation and transrepression when co-expressed with GRα; imbalance between GR-α and GR-β expression is associated with GC insensitivity (26). Cell-specific glucocorticoid responsiveness also involves differential expression of co-receptor proteins functioning as co-activators and co-repressors of transcription. Also, differences in chromatin structure and DNA methylation status of GR-target genes determine cell specific cortisol effects (27). Besides classical genomic and rapid GC-induced non-genomic ligand-dependent steroid receptor actions and crosstalk, there is increasing evidence that the unliganded GR can modulate cell signaling in the absence of glucocorticoids, adding another level of complexity (20).

In sepsis, glucocorticoids may decrease HLA-DR expression on circulating monocytes at a transcriptional level via a decrease in the class II transactivator A transcription (28). Another study found that hydrocortisone treatment reduced the levels of anti-inflammatory cytokines such as soluble TNF

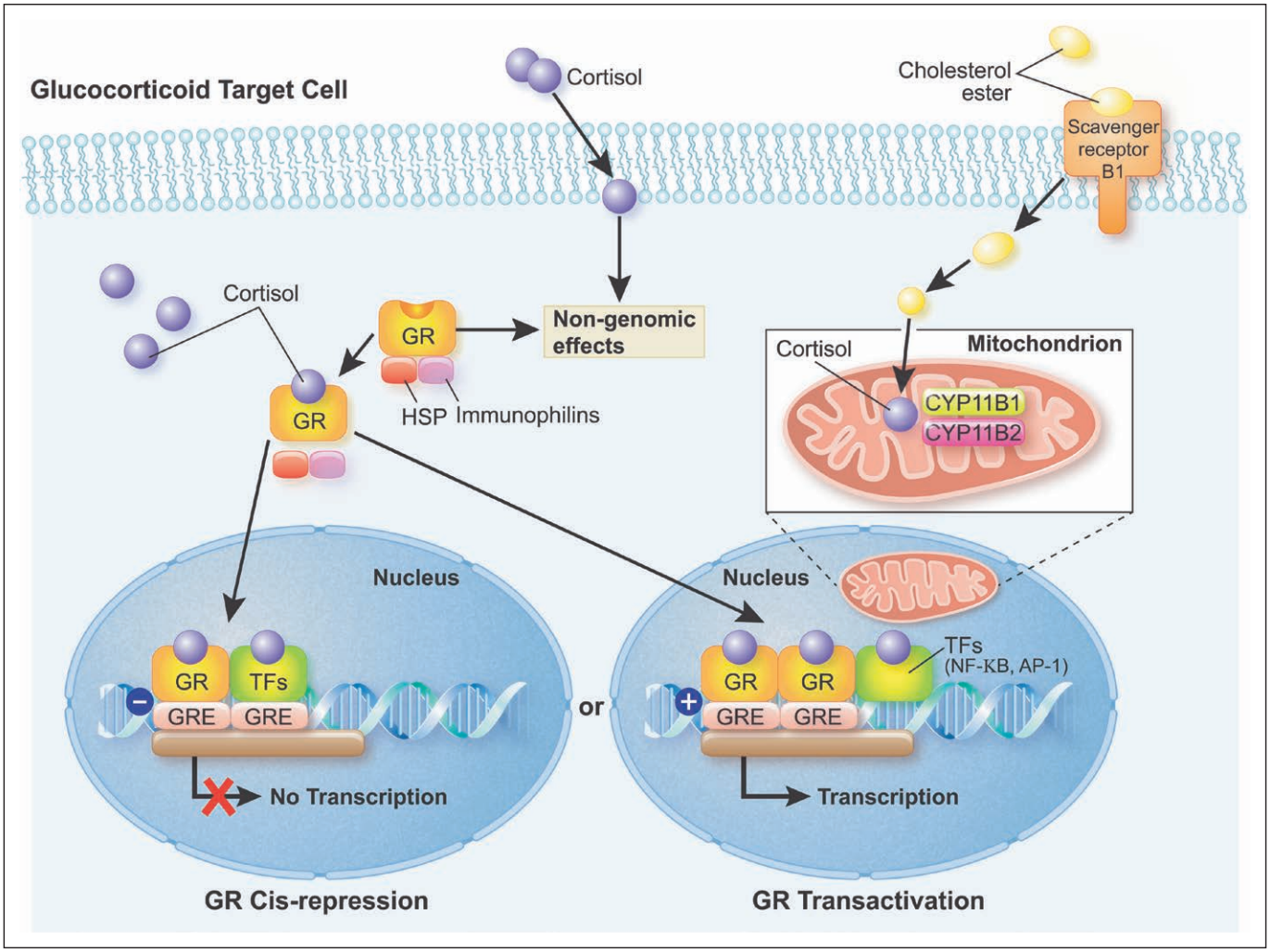

Figure 2. Glucocorticoid synthesis and signalling. Glucocorticoids (e.g., cortisol) are synthesized from cholesterol in the mitochondria by two P450-type enzymes, CYP11B1 and CYPB11B2, and may exert genomic and non-genomic effects. Glucocorticoids diffuse through cell membranes and bind with glucocorticoid receptors (GR, classic GR and MR, mineralocorticoid receptor). Glucocorticoid receptors reside in the cytoplasm in a multiprotein complex with chaperone proteins, heat shock proteins, and immunophilins. The classic GR (specifically GR-α) is the major receptor involved in mediating the glucocorticoid responses to stress and inflammation. Upon binding of cortisol, the GR undergoes a conformational change that allows it to dissociate from the chaperone proteins and translocate into the nucleus and the mitochondria, where it binds to glucocorticoid response elements (GRE) to activate (transactivation) or repress (cis-repression) pro-inflammatory gene expression of various transcription factors (TFs) such as nuclear factor-kappa B (NF-KB) and activator protein-1 (AP-1).

receptors I and II and IL-10, and has only limited effects on HLA-DR expression by circulating monocytes (29).

Dysfunction of the HPA Axis During Critical Illness

Many of the responses normally considered adaptive may be inadequate or counterproductive during severe stress states. Depending on the population of patients studied and the diagnostic criteria, dysfunction of the HPA axis has been estimated to occur at rates from 10%–20% in critically ill medical patients to as high as 60% in patients with septic shock (1).

Evidence from the sepsis (30–34), ARDS (7, 35, 36), and trauma (37, 38) literature suggests that degree of elevation in inflammatory cytokines (e.g., TNF, IL-1β, IL-6) on ICU admission and during ICU stay correlates with disease severity and hospital mortality, and that persistent elevation of cytokines at hospital discharge is associated with adverse long-term outcomes (39).

Cytokine-Induced Activation of the HPA Axis

Inflammatory cytokines including TNF, IL-1 and IL-6 have been shown to activate the HPA axis, especially during sepsis. However, these cytokines do not exert an equivalent effect on CRH release. IL-1 injection is associated with a strong and sustained activation of the HPA axis, while IL-6 and TNF induce weak and transient hypothalamic responses, and IL-2 and interferon-alpha have no effect (40). The route of cytokine administration (intravenous or intraperitoneal) also influences their stimulatory effects on the hypothalamus (41).

It is also likely that cytokines can exert a direct, ACTH-independent effect on adrenal cortisol synthesis (42). The presence of TNF and of its receptors within the adrenal glands suggests that this cytokine plays a role in adrenal function, even though experiments found variably stimulatory (43, 44) or inhibitory (45, 46) effects of TNF on steroidogenesis. Likewise,

IL-1 and its receptor are also produced in the adrenal glands and contribute to steroidogenesis at least partly by regulating prostaglandin pathways (47). Toll-like receptors (TLR), mainly TLR2 and TLR4, are expressed in the adrenal glands and play a critical role in the local immune-endocrine crosstalk in LPS-challenged rodents (48, 49). Further experiments using genetically manipulated mice suggest that immune cells and not steroid-producing cells are key regulators of the immune-endocrine local interaction (49).

Impairment of Adrenal Cortisol Synthesis

Damage to Neuroendocrine Cells. Sepsis is infrequently associated with necrosis or hemorrhage of components of the HPA axis. As a result of the limited venous drainage of the adrenal glands, sepsis-associated massive increase in arterial blood flow to these glands results in enlarged glands (50). Adrenal necrosis and hemorrhage as a consequence of sepsis has been known for more than a century (51). Predisposing factors of the so-called Waterhouse-Friderichsen syndrome include renal failure, shock, disseminated intravascular coagulation, and treatment with anticoagulants or tyrosine kinase inhibitors. Ischemic lesions and hemorrhage have also been described within the hypothalamus or pituitary gland at postmortem examination in septic shock (52).

Altered CRH/ACTH Synthesis. Hypothalamic/pituitary gland stimulation by cytokines, particularly IL-1, induces a biphasic response with initial proportional increase followed by progressive decline in anterior pituitary ACTH concentrations (53, 54). In animal models (55) and in humans (56), sepsis is associated with marked overexpression of iNOS in hypothalamic nuclei that is partly triggered by TNF and IL-1. Subsequent abundant release of NO may cause apoptosis of neurons and glial cells in the neighborhood. Sepsis is also associated with decreased ACTH synthesis, though its secretagogues CRH and vasopressin remained unaltered (57). Thus, the suppression in ACTH synthesis following sepsis may be mediated by NO (58). In addition, feedback inhibition exerted by elevated circulating free cortisol, driven by ACTH-independent mechanisms and suppressed cortisol breakdown, can suppress ACTH (14, 15, 59).

ACTH synthesis can also be inhibited by several therapeutic agents such as glucocorticoids, opioid analgesics, azole antifungals (e.g., ketoconazole) or psychoactive drugs (60). In animals, depending on the dose, timing and duration, opioids have been shown to variably stimulate or inhibit the CRH/ACTH axis, whereas in humans they predominantly inhibit it (61). Both endogenous and exogenous glucocorticoids exert negative feedback control on the HPA axis by suppressing hypothalamic CRH production and pituitary ACTH secretion. This suppression can render the adrenal glands unable to generate sufficient cortisol after glucocorticoid treatment is stopped. Abrupt cessation, or too rapid withdrawal, of glucocorticoid treatment may then cause symptoms of adrenal insufficiency (1, 21). In non-ICU patients, even after a few days of glucocorticoid treatment, removal without tapering leads to adrenal suppression (measured with corticotropin test) in 45% of patients with gradual recovery over a period of 14 days (62). Ample experimental and clinical evidence (29–36) shows that premature discontinuation of glucocorticoids in patients with severe sepsis or ARDS frequently (25%–40%) leads to rebound systemic inflammation and clinical relapse (hemodynamic deterioration, recrudescence of ARDS, or worsening multiple organ dysfunction). Experimental animal sepsis models have demonstrated an early marked increase in ACTH levels that returns to baseline values at around 72 hours (63). Compared with healthy volunteers, clinical studies have found ACTH levels to be significantly lower in critically ill septic patients (14, 64, 65). Decreased ACTH levels are observed during the first week of ICU stay (14, 15). In septic patients, reduction in inflammatory cytokine levels correlates with increases in ACTH levels by ICU day 7 to day 10 (21). Altered ACTH synthesis in response to metyrapone was observed in roughly half of patients with septic shock and very occasionally in critically ill patients without sepsis (64). The reduced ACTH secretion could also be secondary to changes in the feedback regulation of the HPA axis, as described below. Prolonged reduction of ACTH signaling within adrenocortical cells may result in adrenal atrophy (59).

Altered Adrenal Steroidogenesis. The adrenal storage of cortisol is very limited. Thus, an adequate adrenal response to stress relies almost entirely on cortisol synthesis. The HPA axis response to sepsis has not been well defined. There is some evidence that cortisol production rate is somewhat increased in critically ill patients with systemic inflammatory response syndrome (14). As noted earlier, about half of patients with septic shock have decreased cortisol synthesis as assessed by response to the metyrapone test (64). Following administration of metyrapone, 60% of patients with septic shock had 11-deoxycortisol concentrations of less than 7 μg/dL, suggesting decreased corticosteroid synthesis by adrenocortical cells. The alteration may occur at various steps in the cortisol synthesis chain. Histological examination of the adrenal cortex of both animals and humans with sepsis found marked depletion in lipid droplets, suggesting deficiency in esterified cholesterol storage (66). This sepsis-induced loss in lipid droplets is likely mediated by annexin A1 and formyl peptide receptors (67). During critical illness, both increased plasma ACTH concentrations and depletion in adrenal cholesterol stores upregulate adrenal scavenger receptor class B type 1 (SR-B1), an HDL receptor, which captures esterified cholesterol from blood (68). SR-B1-mediated cholesterol uptake is considered as an essential protective mechanism against endotoxin (69). In one study, sepsis induced-deficiency in SR-B1 expression by the adrenal cortex was associated with increased mortality (70).

A number of environmental factors may also have substantial inhibitory effects on adrenal steroidogenesis. Steroidogenesis may be inhibited at various enzymatic steps by drugs, including P-450 aromatase, hydroxysteroid-dehydrogenase, or mitochondrial cytochrome P-450-dependent enzymes (60). In critically ill patients undergoing rapid sequence intubation, the use of etomidate, a drug known to inhibit the last enzymatic

step in cortisol synthesis, increased the risk of adrenal insufficiency between 4 to 6 hours (OR 19.98; 95% CI 3.95 to 101.11) and at 12 hours (OR 2.37; 95% CI 1.61 to 3.47) post-dosing (71). This effect was associated with worsening in organ dysfunction but the ultimate effect on mortality remains unclear. Analgesia and sedation may also affect HPA-axis response in critical illness. Opioids administered to opioid-naive subjects rapidly and profoundly inhibit both stress-related cortisol production and cortisol response to cosyntropin stimulation, while chronic opioid consumers occasionally manifest adrenal crises, phenomena apparently induced by inhibition of the HPA axis at multiple sites (72). Benzodiazepines, similarly, quickly induce diminished cortisol formation by inhibiting activity at multiple central and peripheral sites in the HPA axis, including that of adrenal microsomal 17- and 21-hydroxylase activity as well as 11-β-hydroxylase activity in adrenal mitochondria (73) Finally, experimental studies have shown that inflammatory mediators such as corticostatins may bind to ACTH receptors in the adrenal cortex, thus preventing ACTH stimulation of cortisol synthesis (74).

Altered Extra-Adrenal Corticosteroid Metabolism. There is evidence for altered activity of corticosteroid-metabolizing enzymes during inflammation and critical illness. These changes can influence local tissue action of glucocorticoids and impact the activity of the HPA axis. Even though daytime cortisol production rate is increased in sepsis, the absolute increase appears much less than previously thought. Also, nocturnal cortisol production is not different from that in healthy subjects (15) despite the level of cortisol in the circulation increasing. Several studies have also demonstrated that the half-life of cortisol is dramatically increased during severe sepsis and other critical illnesses (14, 15). All of these findings suggest that reduced cortisol breakdown may be a major feature of sepsis. Experiments involving a range of *in vivo* and *ex vivo* techniques showed that the expression and activity of the glucocorticoid-inactivating 5-reductase enzymes are decreased (14). Additional studies demonstrate that reduced metabolism of cortisol impacted the pulsatile release of ACTH (15). Post-mortem studies of patients who died after prolonged sepsis demonstrate reduced adrenal cortical size and changes in adrenal morphology in keeping with reduced exposure of the adrenal cortex to ACTH (59). These results suggest that some of the long-term changes in the HPA axis associated with critical illness are due to altered metabolism of cortisol that leads to reduced capacity for future cortisol secretion in response to stress. Other studies examining endocrine testing during prolonged critical illness may need re-evaluation in the light of this altered physiology.

Tissue Resistance to Glucocorticoids

Besides the availability of cortisol, the sensitivity of target tissues to cortisol is important in the regulation of cortisol bioactivity. Intracellular glucocorticoid resistance refers to inadequate glucocorticoid receptor alpha (GR-α) activity despite seemingly adequate plasma cortisol concentrations (75). Since the GR-α ultimately controls GC-mediated activity, any condition that affects its binding affinity, concentration, transport to the nucleus, and interactions with GRE (nuclear and mitochondrial) or other relevant transcription factors (NF-kB, AP-1) and co-regulators can eventually affect the response of cells to glucocorticoids (75). Tissue resistance to glucocorticoids has been implicated in chronic inflammatory diseases such as chronic obstructive pulmonary disease, severe asthma, systemic lupus erythematosus, ulcerative colitis, and rheumatoid arthritis (76). Glucocorticoid resistance is also recognized as a potential complication of critical illness, with most of the evidence originating from the sepsis and ARDS clinical and experimental literature (75–81). Critical illness is associated with reduced GR-α density and transcription (7, 25, 82, 83) and increased GR-β (dominant negative activity on GR-induced transcription) (80, 83, 84). These changes are considered maladaptive, since GR-α up regulation was shown to augment the effects of available glucocorticoids (81). Clinical studies in patients with septic shock (79, 80) and ARDS (7) have provided evidence of an association between the degree of intracellular glucocorticoid resistance, disease severity, and mortality.

Ex vivo experiments suggest that, in ARDS, insufficient GC-GRα-mediated activity is a central mechanism for the upregulation of NF-kB activity (7, 81). Plasma samples from patients with declining inflammatory cytokine levels (and thus a state of regulated systemic inflammation) over time elicited a progressive increase in GC-GRα-mediated activity (GRα binding to NF-kB and to glucocorticoid response elements on DNA, stimulation of inhibitory protein IκBα and of IL-10 transcription), and a corresponding reduction in NF-kB nuclear binding, and transcription of TNF-α and IL-1β. In contrast, plasma samples from patients with sustained elevation in inflammatory cytokine levels elicited only modest longitudinal increases in GC-GRα-mediated activity and a progressive increase in NF-kB nuclear binding over time that was most striking in non-survivors (suggesting a dysregulated, NF-kB-driven response). Analysis of lung tissue obtained by open lung biopsy demonstrated that the degree of NF-kB and GRα activation was associated with histological progression of ARDS, with positive correlation between severity of fibroproliferation and nuclear uptake of NF-kB and a lower ratio of GRα: NF-kB nuclear uptake (7). Similarly, in experimental ARDS, lung tissue demonstrated reduced GRα expression and increased GRβ expression, leading to decreased GRα nuclear translocation (84).

The effect of exogenous glucocorticoids on intracellular glucocorticoid resistance was studied in both circulating and tissue cells. In experimental ARDS, low-dose glucocorticoid treatment compared with placebo restored GRα number and function with resolution of pulmonary inflammation (7). Similarly, in an *ex-vivo* ARDS study, prolonged methylprednisolone treatment–contrary to placebo–was associated with upregulation in GRα number, GRα binding to NF-kB, GRα nuclear translocation leading to reduction in NF-kB DNA-binding and transcription of inflammatory cytokines (81).

Treatment with glucocorticoids led to a change in the longitudinal direction of systemic inflammation from dysregulated (NF-kB-driven response, maladaptive lung repair) to regulated (GRα-driven response, adaptive lung repair), with significant reduction in indices of alveolar-capillary membrane permeability and markers of inflammation, hemostasis, and tissue repair.

Sepsis is characterized by decreased GR-α in circulating cells, in liver and muscle (25, 82, 83). In addition, there is decreased GR-α transcription in circulating cells and lymph node/spleen, in liver and kidney, and lung tissue (77). Sepsis is also characterized by an increased expression of the GR isoform GR-β in circulating cells, resulting in an imbalance between GRα and GRβ (80, 83). All these changes are likely to contribute to corticosteroid resistance at a tissue level. Tissue resistance to corticosteroid is highly variable and correlates with severity of illness and mortality (85).

SUMMARY

Three major pathophysiologic events account for CIRCI: dysregulation of the HPA axis, altered cortisol metabolism, and tissue resistance to corticosteroids (**Table 1**). During critical illness, the regulation of cortisol production becomes much more complex, involving multidirectional crosstalk between the CRH/ACTH pathways, autonomic nervous system, vasopressinergic system, and immune system. Recent studies have shown that plasma clearance of cortisol is markedly reduced during critical illness, explained by suppressed expression and activity of the main cortisol-metabolizing enzymes in liver and kidney. Additionally, cortisol production rate in critically ill patients is only moderately increased to less than double that of matched healthy subjects. In the face of low plasma ACTH concentrations, these data suggest that other factors drive hypercortisolism during critical illness, which may suppress ACTH by feedback inhibition. Finally, intracellular glucocorticoid resistance from insufficient GR-α-mediated anti-inflammatory activity (reduced GR-α density and transcription) and an increased expression of GR-β in circulating cells resulting in an imbalance between GRα and GRβ can be found in critically ill patients despite seemingly adequate circulating cortisol levels. These new insights add to the limitations of the current diagnostic tools to identify patients at risk for CIRCI and may also impact how corticosteroids are used in patients with CIRCI.

TABLE 1. Main Mechanisms of Critical Illness-Related Corticosteroid Insufficiency

General defect	Main mechanisms	Key factors
Decrease in cortisol production		
Altered adrenal synthesis of cortisol	Necrosis/hemorrhage	Acute kidney failure; hypo-coagulation; disseminated intravascular coagulation; cardiovascular collapse; tyrosine kinase inhibitors
	Decreased availability of esterified cholesterol	Depletion in adrenal storage regulated by annexin A1–formyl peptide receptors Down regulated scavenger receptor-B1
	Inhibition of steroidogenesis	Immune cells/Toll-like receptors/cytokines
		Drugs (e.g., sedatives, corticosteroids)
		ACTH-like molecules (e.g., corticostatins)
Altered synthesis of CRH/ACTH	Necrosis/hemorrhage	Cardiovascular collapse; disseminated intravascular coagulation; treatment with vasopressor agents
	Inhibition of ACTH synthesis	Glial cells/nitric oxide mediated neuronal apoptosis
		Increased negative feedback from circulating cortisol following up regulation of ACTH-independent mechanisms of cortisol synthesis
		Drugs (e.g., sedatives, anti-infective, psychoactive agents)
		Inappropriate cessation of glucocorticoid treatment
Alteration of cortisol metabolism	Decreased cortisol transport	Down regulation of liver synthesis of cortisol-binding globulins and albumin
	Reduced cortisol breakdown	Decreased expression and activity of the glucocorticoid-inactivating 5-reductase enzymes in the liver with putative role of bile acids; Decreased expression and activity of the hydroxysteroid dehydrogenase in the kidney
Target tissue resistance to cortisol	Inadequate glucocorticoid receptor alpha (GR-α) activity	Multifactorial etiology including reduced GR-α density and transcription and excessive NF-kappa β activation

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Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017

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Dr. Annane has been involved with research relating to this guideline. Dr. Pastores participates in the American College of Physicians: Speaker at ACP Critical Care Update Precourse, the American College of Chest Physicians (CHEST) (faculty speaker at Annual Congress), the American Thoracic Society (ATS): Moderator at Annual Meeting, the European Society of Intensive Care Medicine (EISCM) (co-chair of Corticosteroid Guideline in collaboration with SCCM), and the Korean Society of Critical Care Medicine (co-director and speaker at Multiprofessional Critical Care Board Review Course). He has spoken on the topic of corticosteroid use in critical illness and specifically in sepsis at the International Symposium in Critical and Emergency Medicine in March 2017. Dr. Arlt participates in the Society for Endocrinology UK (Chair of the Clinical Committee, member of Council, member of the Nominations Committee) and the Endocrine Society USA (member, Publication Core Committee). Dr. Briegel participates in the European Society of Intensive Care Medicine, the Deutsche interdisziplinäre Vereinigung Intensivmedizin, and the Deutsche Gesellschaft für Anästhesie und Intensivmedizin, and he has given lectures and talks on hydrocortisone treatment of septic shock. Dr. Cooper participates in a range of specialist societies relating to endocrinology and bone disease. Dr. Meduri disclosed he is a government employee. Dr. Olsen participates in the American College of Clinical Pharmacy (grant review committee), and he represents the American Society of Health-System Pharmacists on the National Quality Forum for Surgery Measures. Dr. Rochwerg disclosed he is a methodologist for ATS, CBS, ESCIM, ASH. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM)" published in parallel.

For more information about this article, Email: pastores@mskcc.org

Objective: To update the 2008 consensus statements for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in adult and pediatric patients.

Participants: A multispecialty task force of 16 international experts in critical care medicine, endocrinology, and guideline methods, all of them members of the Society of Critical Care Medicine and/or the European Society of Intensive Care Medicine.

Design/Methods: The recommendations were based on the summarized evidence from the 2008 document in addition to more recent findings from an updated systematic review of relevant studies from 2008 to 2017 and were formulated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. The strength of each recommendation was classified as strong or conditional, and the quality of evidence was rated from high to very low based on factors including the individual study design, the risk of bias, the consistency of the results, and the directness and precision of the evidence. Recommendation approval required the agreement of at least 80% of the task force members.

Results: The task force was unable to reach agreement on a single test that can reliably diagnose CIRCI, although delta cortisol (change in baseline cortisol at 60 min of $\leq$ 9 µg/dL) after cosyntropin (250 µg) administration and a random plasma cortisol of $\leq$ 10 µg/dL may be used by clinicians. We suggest against using plasma-free cortisol or salivary cortisol level over plasma total cortisol (conditional, very low quality of evidence). For treatment of specific conditions, we suggest using IV hydrocortisone $<$ 400 mg/day for $\geq$ 3 days at full dose in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy (conditional, low quality of evidence). We suggest not using corticosteroids in adult patients with sepsis without shock (conditional recommendation, moderate quality of evidence). We suggest the use of IV methylprednisolone 1 mg/kg/day in patients with early moderate to severe acute respiratory distress syndrome ($PaO_2/FiO_2 < 200$ and within 14 days of onset) (conditional, moderate quality of evidence). Corticosteroids are not suggested for patients with major trauma (conditional, low quality of evidence).

Conclusions: Evidence-based recommendations for the use of corticosteroids in critically ill patients with sepsis and septic shock, acute respiratory distress syndrome, and major trauma have been developed by a multispecialty task force. (*Crit Care Med* 2017; XX:00–00)

Key Words: corticosteroids; glucocorticoids; critical illness; sepsis; septic shock; acute respiratory distress syndrome; major trauma

INTRODUCTION

Critical illness-related corticosteroid insufficiency (CIRCI) is a concept that was first introduced in 2008 by an international multidisciplinary task force convened by the Society of Critical Care Medicine (SCCM) to describe impairment of the hypothalamic pituitary axis (stress response) during critical illness (1). CIRCI is characterized by dysregulated systemic inflammation resulting from inadequate intracellular glucocorticoid-mediated anti-inflammatory activity for the severity of the patient's critical illness. The putative symptoms of CIRCI are listed in **Table 1**. CIRCI is associated with increased circulating levels of biological markers of inflammation and coagulation over time, morbidity, length of ICU stay, and mortality. Given the growing body of evidence that CIRCI occurs across a broad spectrum of critical illness, an understanding of the pathogenesis and treatment of CIRCI is important to all critical care providers.

Two emerging themes made it necessary to revisit the concept, diagnosis, and management of CIRCI (1): the recognition of the importance of evidence-based approaches to patient care to enhance quality, improve safety, and establish a clear and transparent framework for service development and healthcare provision (2); the widespread use of corticosteroids in critically ill patients, highlighting the need for a valid, reliable, and transparent process of evaluation to support key decisions.

Against this background, the SCCM and the European Society of Intensive Care Medicine (ESICM) have updated the 2008 guidelines for the diagnosis and treatment of CIRCI. In addition to rigorous application of GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology, the

TABLE 1. Putative Signs and Symptoms of Critical Illness-Related Corticosteroid Insufficiency (CIRCI)

Clinical	
General	Fever, asthenia
Neurological	Confusion
	Delirium
	Coma
Cardiovascular	Hypotension refractory to fluid resuscitation
	Decreased sensitivity to catecholamines
	High cardiac index
Digestive	Nausea
	Vomiting
	Intolerance to enteral nutrition
Respiratory	Persistent hypoxia
Laboratory	Hypoglycemia
	Hyponatremia
	Hyperkalemia
	Metabolic acidosis
	Hypereosinophilia
Imaging	Hemorrhage or necrosis in hypothalamus, pituitary gland or adrenal gland

recommendations in this document focus on patient-important outcomes and utility to clinicians in everyday practice. It was not intended to define a standard of care, and should not be interpreted as such. As with any clinical practice guideline, it should not be interpreted as prescribing an exclusive course of management. The guideline covers CIRCI in critically ill children and adults. It does not cover chronic adrenal insufficiency and does not apply to neonates, because the guideline panel felt these areas represented separate fields of expertise. This guideline focuses on the three disorders that most clinicians associate with CIRCI: sepsis/septic shock, acute respiratory distress syndrome, and major trauma.

Composition of the Guideline Development Group

A multispecialty task force of international experts in critical care medicine, endocrinology, and guideline methods was convened from the membership of the SCCM and the ESICM. The first in-person meeting was held during the SCCM Critical Care Congress in San Francisco, CA in January 2014, followed by several teleconferences and electronic-based discussion at regular intervals and another three in-person meetings during the annual SCCM Critical Care Congress in January 2015, February 2016, and January 2017. Members who were unable to participate in the in-person meetings were given the opportunity to provide electronic input, and meeting updates were circulated.

Conflict of Interest Policy

We required all guideline task force members to fill out a detailed declaration of interest statement including all current and future financial conflicts of interest (COI) as well as past interests, restricted to the 2 years immediately before joining the guideline development process. No task force members reported any financial COI related to the development and writing of the guideline. All members were allowed to participate in all discussions and had equal weight in formulating the statements or in voting. All were allowed equal involvement in data extraction and writing the rationales. We also allowed members to exclude themselves from discussion and voting around specific questions if they felt significant academic COI. There was no input or funding from industry to produce this guideline. The COI forms are available from the SCCM and ESICM and are updated on a regular basis.

Question Development

The task force members developed a list of questions structured in the Population, Intervention, Comparison, and Outcome (PICO) format regarding the diagnosis and treatment of CIRCI in various clinical conditions (**Supplemental Digital Content 1**, http://links.lww.com/CCM/C914). The methods chair (BR) assisted in developing the PICO questions, i.e., framing the clinical questions in a searchable format. This required careful specification of the patient group (P), the intervention (I), the comparator (C), and the outcomes (O) for intervention questions and the patient group, index tests, reference standard, and target condition for questions of diagnostic test accuracy. For each question the task force agreed upon explicit review question criteria including study design features. Some of these questions had been previously addressed in the 2008 guidelines (1) and required updates of the evidence summaries, whereas others required de novo systematic reviews.

Assessment of Relative Importance of Outcomes

For each intervention question a list of outcomes was compiled, reflecting both benefits and harms of alternative management strategies. Outcomes (from the perspective of a patient) were ranked from "low" to "critical" importance and agreed by consensus of the task force members (**Supplemental Digital Content 2**, http://links.lww.com/CCM/C915). Ranking outcomes by their relative clinical importance helps to focus on those that are most relevant to patients and may lead to improved clarification during potential disagreements in decision making.

SEARCHING FOR EVIDENCE

Sources

The information technologists (based at McMaster University, Hamilton, Ontario) searched The Cochrane Database of Systematic Reviews, DARE, CENTRAL, and Medline for all PICO questions on diagnosis and treatment. All searches were updated through May 2017. The search strategies combined subject headings and text words for the patient population, index test and target condition for the diagnostic questions and subject headings and text words for the population and intervention for the intervention questions (Supplemental Digital Content 1, http://links.lww.com/CCM/C914).

If a previous meta-analysis of high quality was identified which addressed one of the PICO questions, this was used or updated to incorporate new evidence since its publication. Search and screening results were provided to the task force to ensure no important trials were missed or erroneously included.

Reference lists from the included publications were screened to identify additional papers. The methods chair also searched guideline databases and organizations including the National Guideline Clearinghouse, Guidelines International Network, Guidelines Finder, Centre for Reviews and Dissemination, National Institute for Health and Care Excellence, and professional critical care and endocrinology societies for guidelines in order to screen the reference lists.

Selection of Studies for Inclusion

The information technologists screened all titles and abstracts to discard the clearly irrelevant articles. Task force members completed a second screening. References were allocated to pairs of reviewers for evaluation of eligibility. All abstracts that did not meet the inclusion criteria were discarded. Any discrepancies at this stage were resolved by group consensus. All pairs of reviewers, with help from the methods support team, retrieved full texts of potentially relevant studies and examined them independently for eligibility. Any discrepancies were resolved by consensus.

Data Extraction and Critical Appraisal of Individual Studies

For each included study, we collected relevant information on design, conduct, risk of bias, and relevant results. For each

question, the methodologist extracted all individual study data and produced (when pooling was judged to be appropriate) forest plots by outcome. All analysis was done using Review Manager (RevMan) software version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

The risk of bias of the included studies was evaluated using various validated checklists, as recommended by the Cochrane Collaboration (2). These were AMSTAR for systematic reviews (3), the Cochrane Risk of Bias tool for randomized controlled trials (4), and the Newcastle-Ottawa scale for cohort and case-control studies (5).

Evidence Profiles

Evidence summaries for each question were prepared by the methodologist following the GRADE approach (6), using the GRADEpro Guideline Development Tool online software (www.gradepro.org).

The evidence profiles include the summary—pooled or narrative—outcome data, an absolute measure of intervention effect when appropriate, the importance of the outcome, and the summary of quality of evidence for each outcome. Evidence profiles were constructed by the methodologist and reviewed and confirmed with the rest of the task force members.

Rating the Quality of the Evidence for Each Outcome Across Studies

In accordance with GRADE, the task force initially categorized the quality of the evidence (certainty) for each outcome as high if it originated from randomized controlled trials (RCTs) and low if it originated from observational data. We subsequently downgraded the quality of the evidence by one or two levels if results from individual studies were at serious or very serious risk of bias, there were serious inconsistencies in the results across studies, the evidence was indirect, the data were sparse or imprecise, or publication bias was thought to be likely. If evidence arose from observational data, but effect sizes were large, there was evidence of a dose-response gradient, or all plausible confounding would either reduce a demonstrated effect or suggest a spurious effect when results showed no effect, we upgraded the quality of the evidence. By repeating this procedure, we obtained an overall quality of the evidence for each outcome and each intervention.

Formulating Statements and Grading Recommendations

Actionable recommendations. After the evidence summary tables and evidence profiles had been prepared, revised, and approved by the task force, the recommendations were finalized. All recommendations were developed based on the GRADE evidence profiles for each recommendation. Each of the following factors was considered in recommendation development: the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the patient's values and preferences associated with the decision, the implications for resource use and health equity, the acceptability of intervention to stakeholders, and the feasibility of implementation. Recommendations and their strength required the agreement of at least 80% of the task force members. Committee members unable to join the face-to-face meetings or teleconferences were provided opportunity for input electronically. The entire committee agreed on the final wording of each recommendation and rationale with further qualifications for each recommendation (e.g., subgroup considerations, justification, implementation considerations).

Each recommendation was designated either "strong" or "conditional" according to the GRADE approach (7). As outlined by GRADE, we used the phrasing "we recommend" for strong recommendations and "we suggest" for conditional (synonymous with the older term 'weak') recommendations (**Table 2**). The implications of the strength of the recommendations for patients, clinicians, and policy makers are shown in **Table 3**.

Writing Rationale. We collated the actionable recommendations and the clinical advice for each of the clinical questions in separate chapters structured according to a specific format. Each question resulted in one or more specific boxed statements. Within each recommendation the strength was indicated as strong or conditional and the quality of the supporting evidence as high, moderate, low or very low (Table 2).

TABLE 2. Factors Determining Strong vs. Conditional Recommendation

What Should be Considered	Recommended Process
High or moderate evidence (*Is there high or moderate quality evidence?*)	The higher the quality of evidence, the more likely a strong recommendation
Certainty about the balance of benefits vs. harms and burdens (*Is there certainty?*)	The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely a weak recommendation.
Certainty in or similar values (*Is there certainty or similarity?*)	The more certainty or similarity in values and preferences, the more likely a strong recommendation.
Resource implications (*Are resources worth expected benefits?*)	The lower the cost of an intervention compared to the alternative and other costs related to the decision—i.e., fewer resources consumed—the more likely a strong recommendation.

TABLE 3. Implications of the Strength of Recommendation

	Strong Recommendation	Conditional Recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices are likely to be appropriate for different patients, and therapy should be tailored to the individual patient's circumstances. Those circumstances may include the patient or family's values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

All statements are followed by advice for clinical practice, where relevant, and the rationale. The rationale contains a brief section on the relevant background and justification of the topic, followed by a short narrative review of the evidence.

External Review

External peer review was provided through the Board of Regents of the American College of Critical Care Medicine, the councils of the SCCM and ESICM, and the editorial boards of *Critical Care Medicine* and *Intensive Care Medicine*. Two international experts in endocrinology (George P. Chrousos, MD and Stefan R. Bornstein, MD) also reviewed the final draft of the guideline and provided comments.

RECOMMENDATIONS FOR DIAGNOSIS OF CIRCI

1. Is total cortisol response to synthetic adrenocorticotropic hormone (ACTH; cosyntropin) superior to random plasma or serum total cortisol for the diagnosis of CIRCI?

Recommendation: The task force makes no recommendation regarding whether to use delta cortisol (change in baseline cortisol at 60 min of ≤ 9 μg/dL) after cosyntropin (250 μg) administration or a random plasma cortisol of ≤ 10 μg/dL for the diagnosis of CIRCI.

Rationale: The 2008 guidelines suggested that the diagnosis of CIRCI is best made by a delta total serum cortisol of < 9 μg/dL after IV cosyntropin (250 μg) administration or a random total cortisol of < 10 μg/dL (1). To date, however, clinicians have not adopted these diagnostic criteria in their routine practice. Moreover, the latest Surviving Sepsis Campaign guidelines suggest not using the ACTH stimulation test to select patients with septic shock that may be treated with hydrocortisone (8). Nevertheless, a recent guideline from the Endocrine Society confirmed that the high-dose (250-μg) ACTH stimulation test is superior to other existing diagnostic tests to establish the diagnosis of primary adrenal insufficiency, with peak cortisol levels below 18 μg/dL (assay dependent) at 30 or 60 min indicating adrenal insufficiency (9).

We found one single-center randomized trial that compared low-dose ACTH (1 μg) stimulation test with total random cortisol for diagnosis of adrenal insufficiency in 59 adults with septic shock (10). Compared with total random cortisol, the low-dose ACTH test was better able to predict a longer duration of vasopressor requirement and hemodynamic response to corticosteroids. Similarly, prospective cohort studies in adults with or without sepsis (11) and in patients with multiple trauma (12) found that patients with CIRCI, i.e., total cortisol levels < 10 μg/dL or delta cortisol < 9 μg/dL, had poorer outcomes than patients without CIRCI. Likewise, a large multicenter prospective cohort study found that critically ill children with a delta cortisol < 9 μg/dL after the low-dose ACTH stimulation test required higher-dose and prolonged treatment with catecholamines, a higher amount of fluid, and had a higher mortality rate (13). See **Supplemental Digital Content 3** (http://links.lww.com/CCM/C916) for evidence profile.

Owing to the potential for risk of bias in study design, with only one single-center unblinded randomized trial and a small number of prospective cohort studies, and due to imprecision related to low numbers of patients included, we downgraded the quality of evidence to low. After two rounds of voting the task force members could not reach a consensus (> 80% agreement) on whether the ACTH stimulation test is superior to random cortisol for the routine diagnosis of CIRCI. Due to the broad spectrum of abnormalities that may cause CIRCI, the task force thought it is unlikely that a single test can reliably diagnose CIRCI independent of its mechanisms, i.e., altered cortisol synthesis or metabolism, or tissue resistance to cortisol.

2. Is plasma or serum free cortisol level superior to plasma total cortisol level for the diagnosis of CIRCI?

Recommendation: We suggest against using plasma free cortisol level rather than plasma total cortisol for the diagnosis of CIRCI (conditional recommendation, very low quality of evidence).

Rationale: Free cortisol is the bioactive form of cortisol. Critically ill patients often present with low serum concentrations of cortisol-binding globulin (CBG) and hypoalbuminemia. In patients with low serum concentrations of cortisol binding proteins, serum total cortisol levels may not predict serum free cortisol levels, with a correlation between serum levels of free and total cortisol of only 50% to 60% (14).

We found no randomized trial that compared serum total versus free cortisol levels to diagnose CIRCI. A prospective study of 112 critically ill adults with treatment-insensitive hypotension, published after the 2008 recommendations, found a good correlation between serum concentrations of free and total cortisol before and after 250 μg ACTH stimulation testing (15). These findings suggested that using total cortisol levels after ACTH testing is sufficient in critically ill adults. Another prospective cohort study of 69 critically ill patients to assess the time course of serum cortisol levels found that levels of both free and total cortisol predicted clinical outcomes (16). Another prospective cohort study of 29 adults with septic shock found remarkable differences between the serum concentrations of free and total cortisol levels both over time and in response to 1 μg ACTH (17). See Supplemental Digital Content 3 (http://links.lww.com/CCM/C916) for evidence profile.

Measurement of serum free cortisol levels involves cumbersome techniques that are unlikely to be available in all hospital laboratories and unlikely to provide a rapid turnaround time. There were a small number of low-quality observational studies with inconsistent findings. Thus, the task force suggested against measuring plasma free cortisol level over plasma total cortisol level in patients with suspected CIRCI.

3. Is salivary free cortisol level superior to plasma total cortisol level for the diagnosis of CIRCI?

Recommendation: We suggest against using salivary rather than serum cortisol for diagnosing CIRCI (conditional recommendation, very low quality of evidence).

Rationale: In saliva, cortisol is found unbound. Thus, measuring salivary cortisol levels may inform on free cortisol levels and adrenal function. However, salivary cortisol levels may be impacted by a number of confounding factors such as gender, age, time and site of sampling, and saliva volume (18). A few studies evaluated the use of salivary cortisol as a measure for adrenal insufficiency. In one study, free cortisol level was more strongly correlated with salivary than with serum total cortisol in 88 cirrhotic patients (Spearman coefficient 0.91 and 0.76, respectively; $p < 0.001$) (19). In contrast, in a study of 57 patients with septic shock, there was no significant difference between free serum cortisol and salivary cortisol levels ($p = 0.28$) (20). In addition, the correlation between salivary cortisol and total serum cortisol levels was very good (80%). Unbound plasma cortisol can be calculated using total serum cortisol and CBG measurements (21, 22). See Supplemental Digital Content 3 (http://links.lww.com/CCM/C916) for evidence profile.

The evidence demonstrating any benefit of using salivary cortisol over serum cortisol is extremely limited. Although salivary cortisol may be more closely correlated with free cortisol than total cortisol, no study has demonstrated that using salivary cortisol to diagnose CIRCI in critically ill patients leads to improved patient outcomes. Furthermore, the practicality and feasibility of using salivary cortisol is questionable given that it is tested by enzyme immunoassay, which may not be routinely available at most centers. Additionally, there are implementation concerns: in the Estrada-Y-Martin study (20), for example, 19 of the 57 patients were excluded because three initial samples did not provide any saliva, and 16 were eliminated owing to insufficient saliva or blood contamination. The task force therefore felt that using salivary cortisol would not be cost effective, practical, or feasible.

4. Is the 1-μg ACTH stimulation test superior to the 250-μg ACTH test for the diagnosis of CIRCI?

Recommendation: We suggest that the high-dose (250-μg) rather than the low-dose (1-μg) ACTH stimulation test be used for the diagnosis of CIRCI (conditional recommendation, low quality of evidence).

Rationale: The high-dose (250-μg) ACTH stimulation test remains the most popular diagnostic test for adrenal insufficiency. However, this supraphysiologic dose of ACTH may result in significant stimulation of the adrenocortical cells in patients with proven adrenal insufficiency. Therefore, to increase the sensitivity of this diagnostic test, low-dose (1-μg) ACTH was suggested. The high-dose ACTH test is easy to perform and safe. The low-dose ACTH test requires some preparation at the bedside as the commercial ampoules contain 250 μg of ACTH.

A recent meta-analysis of 30 studies, involving 1209 adults and 228 children, found that for secondary adrenal insufficiency, the high- and low-dose ACTH tests had similar diagnostic accuracy (23). The likelihood ratio (LR) of a positive test was 9.1 and 5.9 for the high- and low-dose ACTH test, respectively, for adults and 43.5 and 7.7, respectively, for children. However, both tests had low sensitivity as suggested by the suboptimal LR of a negative test (adults: 0.39 and 0.19 for the high- and low-dose ACTH test, respectively; children: 0.65 and 0.34, respectively). A prospective cohort study of 74 adults with septic shock found that the delta cortisol using the low- and high-dose ACTH tests was equally accurate in predicting vasopressor dependency and mortality (24). Likewise, in a prospective multicenter cohort study of critically ill children, the low- and high-dose ACTH tests showed similar accuracy in the prediction of clinical outcomes (13). See Supplemental Digital Content 3 (http://links.lww.com/CCM/C916) for evidence profile.

Owing to easier practical modalities and the comparable accuracy of the low- and high-dose ACTH tests, the task force suggested using the high-dose rather than the low-dose ACTH test for the diagnosis of CIRCI.

5. Is hemodynamic response to hydrocortisone (50–300 mg) superior to the 250-μg ACTH stimulation test for the diagnosis of CIRCI?

Recommendation: We suggest the use of the 250-μg ACTH stimulation test rather than the hemodynamic response to hydrocortisone (50–300 mg) for the diagnosis of CIRCI (conditional recommendation, very low quality of evidence).

Rationale: Early reports on low-dose corticosteroids in human septic shock hypothesized that hemodynamic improvement unmasks adrenocortical insufficiency (25, 26). Hydrocortisone was found to improve the vasopressor response to norepinephrine in septic patients, this effect being more marked in patients with CIRCI (27). Arterial hypotension may serve as a useful marker of inadequate corticosteroid activity, although not all patients with septic shock may have CIRCI (28).

No studies are presently available that directly address this specific question. CIRCI diagnosed with the 250-μg ACTH stimulation was associated with faster shock resolution in two studies (29, 30). In contrast, the CORTICUS trial found a similar hemodynamic response to corticosteroids in patients with or without CIRCI (31). The recent Hydrocortisone for Prevention of Septic Shock (HYPRESS) trial also did not find a difference in the development of septic shock in the presence or absence of CIRCI (32). However, in the HYPRESS trial only a limited number of patients were screened for CIRCI, affecting the reliability of these data. See Supplemental Digital Content 3 (http://links.lww.com/CCM/C916) for evidence profile.

Earlier shock resolution has been shown to lead to lower mortality (33). However, no studies compared the prognostic value of hemodynamic response to hydrocortisone versus the 250-μg ACTH test for the diagnosis of CIRCI. Meta-analyses examined only differences in mortality rates with corticosteroid treatment between those with and without documented CIRCI (34). Thus, the task force could only recommend the use of the 250-μg ACTH stimulation test to diagnose CIRCI.

6. Is corticotropin level superior to the 250-μg ACTH stimulation test for the diagnosis of CIRCI?

Recommendation: We suggest against using corticotropin levels for the routine diagnosis of CIRCI (conditional recommendation, low quality of evidence).

Rationale: The plasma corticotropin level is determined by corticotropin release from the anterior pituitary gland into the systemic circulation. Normally, plasma concentrations of corticotropin and cortisol change in opposite directions. In primary adrenal insufficiency, plasma cortisol level is low and plasma corticotropin level is high. In hypopituitarism, plasma corticol level is low and plasma corticotropin level is low or normal. During critical illness, plasma corticotropin levels have been variably found to be low, normal, or high and likely follow a dynamic pattern with transiently elevated levels and subsequent decline over a period of weeks after the initial insult (1). We did not find any study that compared the diagnostic accuracy of corticotropin level with that of the ACTH stimulation test.

Owing to the complexity of measuring the plasma level of corticotropin, the task force deemed that it is not feasible in most institutions to obtain a corticotropin level with a sufficiently short turnaround time to have an impact on the acute management of the critically ill.

RECOMMENDATIONS FOR CORTICOSTEROID USE IN CRITAL CARE CONDITIONS

Sepsis

A. Should corticosteroids be administered among hospitalized adult patients with sepsis without shock?

Recommendation: We suggest against corticosteroid administration in adult patients with sepsis without shock (conditional recommendation, moderate quality of evidence).

Rationale: Sepsis and septic shock are major healthcare problems: they affect millions of people worldwide annually and are associated with mortality rates of 25–30% and high direct and indirect costs (35–39). Pro-inflammatory cytokines have been demonstrated to either suppress cortisol response to ACTH or compete with intracellular glucocorticoid function, which can result in CIRCI in septic patients. Sepsis-related CIRCI may in turn precipitate organ failure and result in lack of response to vasopressor therapy in these patients (40, 41). Thus, the potential benefit of corticosteroids for the treatment of sepsis has been tested in dozens of observational studies and trials over a period of several decades.

Analysis of 27 RCTs ($n = 3176$) of patients with sepsis with and without shock revealed a 28-day mortality rate of 29.3% in patients receiving corticosteroids compared with 31.8% in those who received placebo (relative risk [RR] 0.87, 95% CI 0.76–1.0) (42). The quality of evidence was considered low owing to inconsistency in the results and imprecision. See **Supplemental Digital Content 4** (http://links.lww.com/CCM/C917) for evidence profile.

A separate analysis of six RCTs ($n = 826$) of patients with sepsis without shock revealed a 28-day mortality rate of 33.8% in patients receiving corticosteroids compared with 30.6% in those who received placebo (RR 1.11, 95% CI 0.91–1.34) (42). Hyperglycemia was the most common adverse event, and corticosteroids did not increase the risk of secondary infections (RR 1.02, 95% CI 0.87–1.20). The quality of evidence was considered moderate due to imprecision, given the wide confidence intervals. See Supplemental Digital Content 4 (http://links.lww.com/CCM/C917) for evidence profile.

Most recently, the HYPRESS multicenter trial assigned patients with sepsis (excluding those with shock) to receive either a continuous infusion of 200 mg of hydrocortisone for 5 days, followed by dose tapering until day 11 ($n = 190$), or placebo ($n = 190$) (33). The primary outcome was development of septic shock within 14 days. Patients who received hydrocortisone showed no difference in rates of progression to septic shock within 14 days from those given placebo (difference −1.8%; 95% CI −10.7% to 7.2%; $p = 0.70$). In addition, there were no significant differences between the hydrocortisone and placebo groups for the use of mechanical ventilation (53.2% vs 59.9%), mortality at 28 days (8.8% vs 8.2%) or up to 180 days (26.8% vs 22.2%), ICU length of stay (median [interquartile

range] 8 [5–15] vs 9 [6–17] days), or hospital length of stay (median [interquartile range] 26 [16–46] vs 25 [16–40] days). In the hydrocortisone versus placebo groups, 21.5% vs 16.9% had secondary infections, 8.6% vs 8.5% had ventilation weaning failure, 30.7% vs 23.8% had muscle weakness, and 90.9% vs 81.5% had hyperglycemia. Based on these results, the task force members agreed that corticosteroids may not be beneficial in adult patients with sepsis without shock.

B. Should corticosteroids be administered among hospitalized adult patients with septic shock?

Recommendation: We suggest using corticosteroids in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy (conditional recommendation, low quality of evidence).

C. What is the recommended dose and duration of treatment among hospitalized adult patients with septic shock treated with corticosteroids?

Recommendation: If using corticosteroids for septic shock, we suggest using long course and low dose (e.g., IV hydrocortisone ≤ 400 mg/day for at ≥ 3 days at full dose) rather than high dose and short course in adult patients with septic shock (conditional recommendation, low quality of evidence).

Rationale: The latest Cochrane systematic review of the use of low-dose hydrocortisone for treating septic shock, including 33 RCTs with a total of 4,268 patients (42), showed that corticosteroids significantly reduced the risk of death at 28 days compared with placebo. Three of these RCTs included children and the other 30 trials included only adults. Survival benefits were dependent on the dose of corticosteroids, with lower doses (< 400 mg of hydrocortisone or equivalent per day) for a longer duration of treatment (3 or more days at the full dose) found to be better, and on the severity of the sepsis. Furthermore, corticosteroids did not cause harm except for an increased incidence of hyperglycemia and hypernatremia; there was no increased risk of superinfection or gastrointestinal bleeding. See Supplemental Digital Content 4 (http://links.lww.com/CCM/C917) for evidence profile.

A network meta-analysis of 22 trials suggested no clear evidence for the superiority of one type of corticosteroids over another in adult patients with septic shock (43). However, hydrocortisone boluses and infusions were more likely than methylprednisolone boluses and placebo to reverse shock.

Given the consistent effect of corticosteroids on shock reversal and the low risk for superinfection with low-dose corticosteroids, the task force suggests the use of low-dose IV hydrocortisone < 400 mg/day for at least 3 days at full dose, or longer in adult patients with septic shock that is not responsive to fluid and moderate to high-dose (≥ 0.1 μg/kg/min of norepinephrine or equivalent) vasopressor therapy. The task force panel was unable to comment on pediatric patients with septic shock as the meta-analyses we reviewed did not include enough patients in this age group. A small pilot RCT (Steroids in Fluid and/or Vasoactive Infusion Dependent Pediatric Shock, STRIPES) demonstrated the feasibility of a larger RCT to address the role of corticosteroids for the treatment of pediatric shock (44). Since the publication of the Cochrane meta-analysis in 2015, a few small studies of early corticosteroid therapy in patients with pediatric septic shock and adult patients with sepsis-associated ARDS have been published (45–47) but the results are consistent with our current recommendations.

The Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial enrolled 1,241 adult patients with refractory septic shock from 35 centers in France (48). This trial commenced in 2008 and initially included the recombinant form of human activated protein C (APC), drotrecogin alfa-activated. The study featured a 2×2 factorial design with patients assigned to placebo of hydrocortisone + placebo of fludrocortisones + placebo of APC; hydrocortisone + fludrocortisone + placebo of APC; placebo of hydrocortisone + placebo of fludrocortisone + APC; or hydrocortisone + fludrocortisone + APC. Hydrocortisone was administered as a 50-mg IV bolus every 6 h and fludrocortisone as a 50-μg tablet via a nasogastric tube once daily. In 2011, APC was withdrawn from the market after failing to demonstrate adequate efficacy in other clinical trials (49). Once APC was no longer available, the study continued without the APC arms; one arm then comprised placebo corticosteroids (n = 627) and the other arm comprised hydrocortisone and fludrocortisone combined (n = 614). Another large RCT (the ADRENAL study) conducted in Australia and New Zealand enrolled 3,800 patients either to hydrocortisone or to a placebo. Although enrolment is completed, results are not yet available (50). In this trial, no ACTH stimulation testing was performed. The final results of these two trials are still pending but once available may further define the role of corticosteroids in the setting of sepsis or septic shock. Our recommendations may have to be re-addressed once these results are available.

Acute Respiratory Distress Syndrome

Should corticosteroids be administered among hospitalized adult patients with acute respiratory distress syndrome?

Recommendation: We suggest use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (PaO_2/FiO_2 of ≤ 200 and within 14 days of onset) (conditional recommendation, moderate quality of evidence).

Rationale: Acute respiratory distress syndrome (ARDS) represents an important public health problem globally. Despite advances in supportive care, ARDS is associated with a high mortality rate (35%–45%) (51). ARDS is also associated with high costs of inpatient care and significant long-term morbidity and resource utilization (52). In ARDS, prolonged mechanical ventilation is associated with increased risk of disability and mortality at 1 year (53, 54).

Nine trials have investigated prolonged glucocorticoid treatment in ARDS (46). One of these trials was in patients with ARDS due to community-acquired pneumonia (59) and another was a subgroup analysis of the initial corticosteroid trial in septic shock (60). These trials consistently found that glucocorticoid treatment was associated with a significant reduction in markers of systemic inflammation (inflammatory cytokines and/or C-reactive protein levels), reduction in the duration of mechanical ventilation by approximately 7 days, and probable

reduction in hospital mortality by approximately 7% and 11% in patients with mild and severe ARDS, respectively (moderate certainty) (61). All but two trials (55, 56) investigated treatment initiated in early ARDS. Compared with late (≥ 7 days) initiation, early (< 72 h) initiation of methylprednisolone treatment–when fibroproliferation (62) is still in the early stage of development (cellular with predominant type III procollagen)–shows response to a lower daily methylprednisolone dose (1 mg/kg/day vs 2 mg/kg/day) and is associated with faster disease resolution (e.g., shorter time to unassisted breathing, shorter time to ICU discharge) (61). See Supplemental Digital Content 4 (http://links.lww.com/CCM/C917) for evidence profile.

A recent individual patient data (IPD) analysis of the four largest trials ($n = 322$) investigating prolonged methylprednisolone treatment in early (57, 58) and late (on and after day 7 of onset) (55, 56) ARDS confirmed trial-level data demonstrating benefit with corticosteroids, with improved survival and decreased duration of mechanical ventilation (61).

With the exception of hyperglycemia (mostly within the 36 h following an initial bolus), prolonged glucocorticoid treatment was not associated with increased risk for neuromuscular weakness, gastrointestinal bleeding, or nosocomial infection (61). Hyperglycemia was not associated with increased morbidity. Two trials reported a significant reduction in the risk for developing shock (56, 59).

The task force members believed that the quality of the evidence for the effect of corticosteroids on mortality was moderate, given the serious risk of imprecision related to small numbers of events and confidence intervals that approach no effect. Some of the included trials allowed blinded crossover, two trials were unblinded, and four trials had less than 60 patients.

In summary, the task force suggested that methylprednisolone be considered in patients with early (up to day 7 of onset; PaO_2/FiO_2 of < 200) in a dose of 1 mg/kg/day and late (after day 6 of onset) persistent ARDS in a dose of 2 mg/kg/day followed by slow tapering over 13 days (**Supplemental Digital Content 5**, http://links.lww.com/CCM/C918). Methylprednisolone is suggested because of its greater penetration into lung tissue and longer residence time (63). Furthermore, methylprednisolone should be weaned slowly (6–14 days) and not stopped rapidly (2–4 days) or abruptly as deterioration may occur from the development of a reconstituted inflammatory response. Finally, glucocorticoid treatment blunts the febrile response; therefore, infection surveillance is recommended to ensure prompt identification and treatment of hospital-acquired infections.

Major Trauma

Should corticosteroids be administered among hospitalized adult patients with major trauma?

Recommendation: We suggest against the use of corticosteroids in major trauma (conditional recommendation, low quality of evidence).

Rationale: Major trauma is the main cause of non-septic systemic inflammatory response syndrome (SIRS). Tissue necrosis, hemorrhage and ischemia–reperfusion injury are the main factors that trigger the inflammatory cascade. CIRCI may be common in severe trauma patients, and is associated with uncontrolled inflammation, vasopressor dependency and poor clinical outcomes (64).

We found 19 trials ($n = 12,269$) that investigated the effects of corticosteroids on short-term mortality in adults with multiple trauma. There were 1,691/6,286 (26.9%) deaths in the corticosteroid group versus 1,401/5,983 (23.4%) deaths in the placebo group (RR = 1.00, 95% CI 0.89–1.13). Stratified analysis of mortality based on corticosteroid dose (low vs high) found no significant dose effect (test for interaction $p = 0.73$). The RR of dying was 1.03 (95% CI 0.86–1.22) in the 10 trials that examined low-dose corticosteroid treatment and 0.98 (95% CI 0.81–1.18) in the nine trials of high-dose corticosteroids. Corticosteroid therapy did not increase the risk of gastroduodenal bleeding ($n = 12$ trials; RR = 1.22, 95% CI 0.90–1.65) or superinfection ($n = 7$ trials; RR=0.93, 95% CI 0.80–1.08). Two trials examined the effects of hydrocortisone (65) and hydrocortisone plus fludrocortisone (66) specifically in trauma-associated CIRCI, as defined by a change in baseline cortisol at 60 min of < 9 μg/dL after cosyntropin (250 μg) administration. In the first trial ($n = 113$ multiple trauma patients with CIRCI), hydrocortisone therapy prevented the development of hospital-acquired pneumonia by day 28 (hazard ratio [HR] 0.47, 95% CI 0.25–0.86) and increased by 6 days (95% CI 2–11) the number of mechanical ventilation-free days. In the second trial ($n = 267$ head trauma patients with CIRCI), the HR for hospital-acquired pneumonia with corticosteroids versus placebo was 0·80 (95% CI 0.56–1.14). In this trial, there was no interaction between response to corticosteroid therapy and CIRCI status. See Supplemental Digital Content 4 (http://links.lww.com/CCM/C917) for evidence profile.

The largest trials which primarily drive the signal for mortality outcome were at low risk of bias, and stratified analysis found no dose effect. Although the type of patients and the formulation, dose, and duration of corticosteroids varied fairly widely across trials, there was no evidence for significant inconsistency in the results. Although it appears that corticosteroids have no effect on mortality in trauma patients, the imprecision of pooled results does not allow exclusion of a potential for benefit or harm from corticosteroid therapy. The task force members judged the overall quality of evidence for this question as low. Given the potential for clinically important side effects with treatment, the task force made a conditional recommendation against corticosteroids for major trauma until further data are available supporting its use.

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