ABSTRACT

Adrenal insufficiency (AI) is a frequently discussed but inadequately understood condition among critically ill patients. Increased glucocorticoid action is an essential component of the stress response. Dysfunction of the HPA axis in critical illness may be best described by the term critical illness–related corticosteroid insufficiency (CIRCI), in preference to terms like absolute or relative adrenal insufficiency. Most of the research about CIRCI has focused on patients with septic shock and acute respiratory distress syndrome (ARDS). The diagnosis of CIRCI relies on clinical suspicion and ACTH stimulation test results. Adjunctive corticosteroids may be considered in patients with septic shock who have responded poorly to volume resuscitation and catecholamines, and for patients with ARDS. No high-quality data supporting such intervention for children is currently available. Routine ACTH testing is not recommended to identify this subset of patients with septic shock who should receive hydrocortisone therapy. Given the lack of consistent benefit and likely under appreciation of the adverse effects of this drug class, clinicians should maintain equipoise for well-designed clinical interventional trials addressing both the potential benefits and risks of adjunctive corticosteroids prescribed for septic shock and ARDS.

Keywords: Adrenal insufficiency, critical illness related corticosteroid insufficiency, CIRCI, adrenocorticotropic hormone, ACTH, glucocorticoids, corticosteroids, septic shock, acute respiratory distress syndrome, critical illness
**Introduction**

Critical illness represents a major challenge for the human body where an adequate stress response is indispensable for healing and survival. Typically, cortisol synthesis increases in relation to magnitude of the stress response, but critically ill patients may manifest glucocorticoid insufficiency at some stage, that may include both a decrease in glucocorticoid synthesis and peripheral glucocorticoid resistance. One of the more controversial areas in critical care in recent decades relates to the issue of adrenal insufficiency (AI) and its treatment in critically ill patients. There is no consensus on which patients to test for AI, which tests to use and how to interpret them, whether to prescribe corticosteroids, and, if so, who to treat and with what dose. The diagnosis of AI is challenging, because it often occurs insidiously and its symptoms may be nonspecific or masked by ongoing critical illness. Diagnosis of AI has most typically relied on assessment of plasma cortisol before and after administration of exogenous cosyntropin (corticotropin, an ACTH analogue). This review illustrates the complexity and diversity of pathophysiological changes in glucocorticoid secretion, metabolism, action and how these are affected by various types of illness and management of AI in a variety of critical illnesses encountered in pediatric intensive care units (PICU).

**Physiology**

The regulation of glucocorticoid secretion is primarily mediated by neurosecretory neurons located in the nucleus paraventricularis of the hypothalamus. These neurons secrete corticotropin-releasing hormone (CRH), the key regulator in control of hypothalamic-pituitary-adrenal (HPA) axis function, which stimulates and is stimulated by noradrenergic neurons of the central sympathetic stress system. CRH triggers the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland as the pro-peptide, pro-opiomelanocortin. Upon ACTH stimulation, glucocorticoids are synthesized de novo mainly from cholesterol within the zona fasciculata of the adrenal cortex. Since the rate of secretion is directly proportional to the rate of biosynthesis, any disruption of the pathway may result in decrease glucocorticoid release. Over 90% of the cortisol released is bound to the cortisol-binding globulin (CBG) or albumin which facilitate the transport and controlled release of cortisol to target tissues. Remaining unbound cortisol, approximately 10% of the total represents the bioactive form. Cleavage of CBG, which may occur at the (inflamed) tissue level by neutrophil-elastase, liberates cortisol which then can enter the cell and bind to the intracellular glucocorticoid receptor. Availability of bioactive cortisol is directly related to the concentration of CBG and to a lesser degree to the concentration of albumin, which has a high capacity and a low affinity for binding cortisol. Accordingly, CBG levels are inversely correlated with the cortisol disappearance rate, which may be prolonged in chronic critical illness.\(^1\)\(^2\)

**The hypothalamic-pituitary-adrenal axis**

One of the body’s most important regulatory systems needed to achieve these responses is the hypothalamic-pituitary-adrenal (HPA) axis (Fig. 1). Activation of the HPA axis during severe stress such as critical illness ultimately leads to secretion of glucocorticoids as its primary product. Cortisol production and secretion is stimulated mainly by ACTH produced in the anterior
pituitary. ACTH also stimulates the production of adrenal androgens and, to a lesser extent, of mineralocorticoids.\textsuperscript{2} The main stimulators of ACTH production are CRH and arginine vasopressin (AVP), which are secreted by the hypothalamus. Catecholamines, angiotensin II, serotonin, and vasoactive intestinal peptide (VIP) are also known stimulators of ACTH secretion. In addition, some pro-inflammatory cytokines stimulate ACTH secretion: interleukin-1 (IL-1), IL-2, IL-6, and tumor necrosis factor $\alpha$ (TNF-$\alpha$), whereas others inhibit (e.g., transforming growth factor-$\alpha$).\textsuperscript{3-5} Many factors modulate CRH secretion, including adrenergic agonists, opioids, and inflammation cytokines (IL-1, IL-2, IL-6, and TNF-$\alpha$). Finally, the hypothalamic-pituitary axis is kept in balance by the negative feedback effect of cortisol. The secretion of the hypothalamic-pituitary axis hormones (ACTH, CRH, and AVP) follows a pulsatile pattern with a circadian rhythm, resulting in highest cortisol concentrations in the morning. This cortisol diurnal rhythm is lost in critical illness. The amount of glucocorticoid found in adrenal tissue is not sufficient to account for the initial increase in cortisol that occurs following stress, and it is not sufficient to maintain normal rates of secretion for more than a few minutes in the absence of continuing biosynthesis. The rate of secretion is thus directly proportional to the rate of biosynthesis. Any disruption in glucocorticoid synthesis immediately results in decreased plasma corticosteroid concentrations.\textsuperscript{6-7}
Figure 1. Activity of the hypothalamic-pituitary-adrenal axis under normal conditions (Panel A), during an appropriate response to stress (Panel B), and during (seemingly) inappropriate response to critical illness (Panel C).33

**Actions of glucocorticoids**

The main glucocorticoid, cortisol is vitally important for cardiovascular reactivity, capillary integrity, metabolism, and anti-inflammatory effects.8 Cortisol has a supportive role in the maintenance of vascular tone, and potentiates cardiac contractility as well as vasoconstrictory actions of catecholamines. Amino acids derived from lean body catabolism facilitated by cortisol atroigene activation, are used for gluconeogenesis, acute phase reactant synthesis and expansion of the immune system. Beta-oxidation of cortisol-facilitated free fatty acid provides ATP to fuel aerobic glycolysis. Cortisol anti-inflammatory effects include decreased capillary permeability, decreased numbers, migration and reactions of white blood cells into the inflamed area, and modulated cytokine production.9 Essentially most aspects of immune function are modulated by cortisol.
Pathogenesis of adrenal insufficiency:

A) Decreased production of glucocorticosteroids

AI can be considered primary or secondary, although this categorization is often artificial within the context of critical illness. Secondary AI may result from irreversible anatomic damage to the hypothalamus or the pituitary gland, inducing a decreased CRH or ACTH synthesis. During critical illness, many factors can impair the cortisol response to ACTH. Cortisol synthesis can be impaired by (pre-existing) disease of the hypothalamus, pituitary or adrenals, by administration of drugs, by inflammatory cytokines and infection, by tissue resistance to cortisol, by substrate deficiency, or by decreased cortisol delivery.

Substrate deficiency for cortisol synthesis may also lead to a decreased production of cortisol during acute illness. As described, the rate of cortisol secretion is directly proportional to the rate of biosynthesis from cholesterol. Since the adrenals do not store any cholesterol, the main sources of cholesterol for steroid formation are plasma lipoproteins. However, in critical illness, total and high-density lipoproteins (HDL) levels are low, and low HDL levels are reported to be associated with a diminished response to ACTH in the critically ill. In the acute phase of critical illness, amounts and activity of serum protein including CBG are markedly reduced, resulting in increased availability of free and biologically active serum cortisol. However, it may also result in diminished distribution and delivery of cortisol to the site of inflammation, immune cells and other target organs. In the prolonged phase of critical illness, CBG levels may increase concordant with decreasing free cortisol levels.

Necrosis of the hypothalamus or the pituitary gland has been reported in patients with sepsis with resultant decreased synthesis of CRH and ACTH. This necrosis often develops because of insufficient oxygen supply due to prolonged hypotension or severe coagulation disorders. Furthermore, patients with critical illness such as sepsis may develop adrenal insufficiency due to bilateral necrosis or haemorrhage of the adrenals. This phenomenon is well-known in the Waterhouse – Friderichsen syndrome characterised by meningococcal infection, although other pathogens have also been associated with adrenal haemorrhage and insufficiency in disseminated infection. With increasing vaccination for meningococcus, pneumococcus and hemophilus, adrenal apoplexy as a deadly aspect of pediatric septic shock is now much less common. Furthermore, high levels of inflammatory cytokines can lead to impaired cortisol synthesis. For example, TNF-α impairs CRH-stimulated ACTH-release and inhibits the stimulatory actions of ACTH on the adrenals in cortisol synthesis. Because of increasing new born screening for 25-hydroxylase deficiency, responsible for 95% of congenital adrenal insufficiency, and rare autoimmune Addison disease, primary adrenal insufficiency in children is unusual.

Numerous drugs used in intensive care units during critical illness are known to compromise cortisol synthesis. A frequent cause is chronic and acute treatment with corticosteroids which induces prolonged suppression of the HPA axis. Other drugs block enzymatic steps in cortisol synthesis such as inhibition of adrenal 11β-hydroxylase by the anaesthetic etomidate, or the anti-fungals ketoconazole or high-dose fluconazole. Cortisol metabolism may be accelerated by antimicrobial drugs such as rifampicin, cyclosporine, clarithromycin and antiepileptic drugs such as phenytoin and phenobarbital.
B) Peripheral resistance to glucocorticoids

Proinflammatory cytokines and sepsis have been demonstrated to modulate numbers, expression and function of the glucocorticoid receptor. Inappropriate response to inflammation can be aggravated by tissue resistance to glucocorticoids. Several factors might be involved and are probably interacting:

- Decreased access of cortisol to the inflammatory site secondary to the reduction of circulating CBG
- Modulation of local cortisol level by a reduction of the cleavage of CBG-cortisol complex (anti-elastase activity)
- Reduction of the number and the affinity of glucocorticoid receptors, increase in the conversion of cortisol to inactive cortisone by an increased activity of the 11-β-hydroxysteroid dehydrogenase stimulated by IL-2, IL-4, and IL-13.

These different mechanisms can account for a decreased activity of glucocorticoids, whereas serum cortisol may be appropriate.21

Critical Illness–Related Corticosteroid Insufficiency

It is important to distinguish between patients with pre-existing dysfunction of the HPA axis (chronic steroid use, Addison’s disease) and patients who develop (acute) adrenal insufficiency because of severe illness or injury. Although highly activated, the HPA axis activity can be insufficient for the degree of stress, a state which may be denoted as relative adrenal insufficiency (RAI), in which serum cortisol levels, although high in absolute terms, are insufficient to maintain homeostasis. RAI seems to be related to an increased risk of death, although this is under debate.15,22 There has recently been a great deal of interest regarding the assessment of adrenal function and the indications for corticosteroid therapy in critically ill patients.23 In addition, analysis of serum total cortisol levels in critically ill patients suggested more often a state of RAI than when analysing free cortisol levels. The latter removes confounding factors due to low protein levels, which is often the case in the critically ill, and suggests that many patients had in fact normal adrenal function.24 These complex findings led to diminished popularity of the term ‘adrenal insufficiency’ in the intensive care unit (ICU).

However, one could argue on the terms ‘absolute’ and ‘relative’ adrenal insufficiency in the context of critical illness, because the distinction between these two entities is artificial and not always clear. Dysfunction of the HPA axis in critical illness may be best described by the term, critical illness–related corticosteroid insufficiency (CIRCI) and terms absolute or relative adrenal insufficiency are best avoided in the context of critical illness.25 CIRCI is defined as inadequate cellular corticosteroid activity for the severity of the patient’s illness. CIRCI may manifest with insufficient glucocorticoid (GC)-glucocorticoid receptor (GR)–mediated down-regulation of proinflammatory transcription factors, leading to persistent elevation of proinflammatory mediators over time. Adrenal insufficiency may arise due to dysfunction at any point in the HPA axis. 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 their illness).26-28 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. On the other hand, many critically ill children with low circulating cortisol, total or free, may not demonstrate clinical signs of corticosteroid insufficiency. It remains difficult to discern if a low cortisol concentration in a critically ill patient truly represents an insufficiency or another adaptive host response.

**Diagnosis**

Patients with chronic adrenal insufficiency such as congenital adrenal insufficiency or Addison’s disease usually present with a history of fatigue, weakness, weight loss, anorexia, and gastrointestinal disturbances such as nausea, vomiting, abdominal pain and diarrhea. Clinical signs may be more specific and include hyperpigmentation (primary adrenal insufficiency) and orthostatic hypotension. Laboratory findings in glucocorticoid deficiency can demonstrate a mild normocytic anaemia, lymphocytosis, eosinophilia, hyponatremia, hyperkalemia and hypoglycemia. However, these features may be hard to recognize in the critically ill and most of the times are absent. In CIRCI, the main diagnostic clue may be refractory hypotension resistant to vasoactive-inotropic drugs, despite adequate fluid reuscitation. CIRCI should be at least considered in critically ill patients requiring vasoactive-inotropic support, particularly when displaying a hyperdynamic circulation profile. Laboratory assessment may demonstrate eosinophilia and hypoglycemia, while other findings associated with chronic adrenal insufficiency are uncommon. However, not all children with impaired hemodynamics are adrenally insufficient and not all children with low circulating cortisol have impaired hemodynamics.

**ACTH stimulation test**

The gold standard in the assessments of secondary adrenal insufficiency, the insulin tolerance test, stressing the adrenals with hypoglycaemia, and the metyrapone test, inhibiting the enzymatic reaction of 11-deoxycortisol to cortisol and measuring the ability of the pituitary gland to release ACTH in response to decreased blood cortisol levels, have obvious limitations for patients and clinicians in the critical care setting. Therefore, the most favoured method of diagnosing the HPA response to stress and CIRCI is dynamic adrenal testing with the standard dose, short corticotropin stimulation test, in which 250 µg of synthetic ACTH is intravenously administered, and serum cortisol levels quantified before, and 30 and 60 minutes afterwards ACTH administration. The identification of a minimal threshold level below which CIRCI is likely and a maximal threshold level above which AI is unlikely would be clinically useful. However, many threshold levels have been proposed for the definition of an insufficient cortisol concentration (measured at any time of day) during acute illness, but none is entirely satisfactory.

Proposed minimal levels have ranged from 10 µg/dL (276 nmol/L) to 34 µg/dL (938 nmol/L), but several studies have suggested that a threshold of 15 µg/dL (414 nmol/L) may best identify patients who have clinical features of CIRCI or who might benefit from cortisol replacement therapy. The incremental response after the administration of corticotropin, in contrast to the response found in patients who are not critically ill, may have prognostic implications. A small increase, less than 9 µg/dL (250 nmol/L), from the baseline cortisol level to the highest cortisol level (measured at 30 or 60 minutes) is associated with an increased risk
for death. CIRCI seems to be unlikely when a random cortisol measurement is greater than 34 µg/dL. Conversely, CIRCI is more likely if the serum cortisol level is less than 15 µg/dL during acute severe illness. For patients who have cortisol levels between these two values, a poor response on a corticotropin test (increase less than 9 µg/dL) would indicate the possibility of CIRCI and possible need for supplemental corticosteroids in the appropriate clinical setting. [Figure 2]33 Lastly, an appropriate increase of cortisol levels (> 9 µg/dL) in patients presenting high basal levels (> 34 µg/dL) associated with clinical features compatible with adrenal failure may suggest tissue resistance to glucocorticoid. It is important to be aware that even in patients who have normal test results, CIRCI may develop later in the illness. Similarly, patients with low random or ACTH simulated cortisol concentrations, need not necessarily demonstrate clinical signs of adrenal dysfunction. It is unclear how often one should perform such tests, but the development of new clinical features suggesting CIRCI or a deterioration in clinical condition should prompt consideration of further testing. However, rapid deterioration of clinical status often results in empiric corticosteroid administration, rather than testing and watchful waiting.

Figure 2. One approach to investigation of adrenal corticosteroid function in critically ill patients based on
Several studies have suggested, that a 1µg dose (low-dose corticotropin stimulation test) of corticotropin is more sensitive for diagnosing AI than the 250µg dose of corticotropin. However, the use of this test to diagnose CIRCI remains controversial, because no consensus has been reached about the dose of ACTH administered and appropriate cut-off levels for the diagnosis of CIRCI, and therefore the prognostic value regarding mortality and corticosteroid treatment with this approach. Indeed, the usual but rather high dose of 250 µg of ACTH results in supra physiological plasma concentrations of ACTH, but administration of 1 µg of ACTH, introduced as a more sensitive test, has been reported to give only slightly improved sensitivity.13 Assays are not uniform and show variations in test characteristics, and a wide variety of criteria is used to define CIRCI in the critically ill patients: from random cortisol levels (without or prior to ACTH testing), to peak cortisol values (after corticotropin testing), to increments from baseline to peak cortisol level after corticotropin, all with many variable cut off levels used. However, random cortisol levels are determined by the activity of the entire HPA axis and have a broad reference range in the healthy adult population like those in the critically ill.17 Recent consensus recommendations suggest a diagnosis of adrenal insufficiency in critically ill patients is best made by a rise in total serum cortisol of <9 µg /dL after corticotropin (250 µg) administration or a random total cortisol of <10 µg /dL.25 However, it needs to be appreciated that the quality of evidence as a basis for such recommendations in children is very low.

It has not been established whether a random cortisol adequately reflects the 24-hour secretory profile in the critically ill. Plasma cortisol values measured hourly over a 24-hour period revealed spontaneous hourly fluctuations (both rises and falls) from baseline cortisol values. In certain instances, the spontaneous rises in cortisol even exceeded those induced by exogenous ACTH. Thus, depending on the time of sampling for random cortisol, a patient may be classified as adrenal sufficient or insufficient. These data suggest that a diagnosis of adrenal insufficiency based on single point cortisol estimation may be inaccurate in the critically ill. In terms of diagnosing CIRCI, it should be appreciated that even 50% of healthy volunteers have a cortisol increase following corticotropin of less than 9 µg/dL (250 nmol/L). Another difficulty in ACTH testing is the interpretation of total serum cortisol levels. It is accepted that free rather than protein-bound cortisol levels are responsible for cortisol’s physiological activity. Real time fractionated free cortisol quantification by modern techniques is now feasible to help guide clinical decision making for cortisol replacement therapy. However, quantification of free cortisol remains cumbersome, is possible only in limited research institutions, and is not routinely available. When corticosteroid binding proteins in serum fall, as often occurs during critical illness, the patient may be misdiagnosed as adrenal insufficient due to lower serum total cortisol levels, although serum free cortisol levels may be normal or even elevated. Furthermore, the normal range of free cortisol among critically ill patients is remains unclear. Finally, corticotropin testing may have poor reproducibility. For example, during severe sepsis and septic shock, low random cortisol concentrations and high proportional changes between unstimulated and corticotropin-stimulated cortisol concentrations measured on day 1 of admission correlated with ICU and hospital stay but not to mortality. When these measures were repeated on day 2 no correlations were noted with any of these end-points. At this time, the diagnosis of tissue corticosteroid resistance remains problematic.
Therapy

Treatment with corticosteroids in patients with CIRCI may have beneficial effects by improving hemodynamics (reduction in vasoactive-inotropic support) and providing systemic anti-inflammatory activity. Adjunctive corticosteroids prescription for pediatric septic shock seems logical with scientific rationale. However, contemporary investigations have highlighted the need to consider not only the beneficial hemodynamic and anti-inflammatory properties of corticosteroids, but also the catabolic and immunodeficiency characteristics of this drug class. This is particularly relevant given the recent emphasis on the compensatory anti-inflammatory characteristics of sepsis including risk for immunoparalysis. In the first contemporary study of low-dose adjunctive hydrocortisone for adult septic shock, more rapid shock reversal was noted in patients treated with hydrocortisone (200-300 mg/day), particularly in patients with CIRCI, the so-called non-responders to the corticotropin stimulation test. Moreover, mortality was reduced in non-responders treated with hydrocortisone therapy compared to non-responders receiving placebo, while there were no differences in groups in responders. However, in a follow-up investigation, CORTICUS, the beneficial effect of hydrocortisone for adult septic shock was not ascertained, and in addition the corticotropin stimulation test did not identify the group of patients most likely to benefit from hydrocortisone replacement therapy. No high quality interventional trials examining adjunctive hydrocortisone therapy prescribed for refractory pediatric septic shock have been published.

On the other hand at least eight descriptive studies have concluded no benefit or potential harm associated with adjunctive corticosteroids prescribed to children with septic shock. For example, a retrospective cohort study examining the clinical database derived from the RESOLVE (REseaching severe Sepsis and Organ dysfunction in children: a gLobal perspective, F1K-MC-EVBP) trial of activated protein C for pediatric severe sepsis reported that children with severe sepsis who received adjunctive corticosteroid therapy exhibited similar illness severity compared with those who did not, but that no definitive improvement in outcomes could be attributable to adjunctive corticosteroid therapy in this largest pediatric sepsis trial conducted to date. Whether random cortisol levels or responses to ACTH predict reduction of mortality by hydrocortisone therapy in septic shock remains under debate.

In contrast, in some adult studies examining other critical illnesses such as liver failure and during weaning from mechanical ventilation, treatment with hydrocortisone improved survival and successful ventilatory weaning. The 2014 American College of Critical Care Medicine Guidelines for Hemodynamic Resuscitation for Pediatric and Neonatal Sepsis recommend that hydrocortisone should be considered in the management strategy of children with septic shock, particularly those patients who have responded poorly to fluid resuscitation and vasopressor agents, but that corticotropin testing is not useful in identifying the subset of patients with septic shock who should receive hydrocortisone therapy. If a child is “at risk of absolute adrenal insufficiency or adrenal pituitary axis failure” (e.g., purpura fulminans, congenital adrenal hyperplasia, prior steroid exposure, hypothalamic/pituitary abnormality, intubation with etomidate induction) and remains in shock despite epinephrine or norepinephrine infusion, then hydrocortisone can be administered (1mg/kg or 30 mg/m$^2$) intravenously every 6 hours) ideally after attaining a blood sample for subsequent determination of baseline cortisol concentration. These pediatric recommendations are based on expert opinion and are not evidence-based.
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 in adults. For adults, methylprednisolone in a dose of 1 mg/kg/day for >14 days is recommended in patients with severe early acute respiratory distress syndrome.²⁵

Such, moderate-dose glucocorticoid therapy should be considered in the management strategy of patients with severe acute respiratory distress syndrome (ARDS) because of a survival benefit when initiated before day 14 of ARDS, but again, corticotropin stimulation testing is not useful.⁶⁴ 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.²⁵

Practitioners prescribing replacement corticosteroid, should be aware of not only the anti-inflammatory and hemodynamic stabilizing properties of the class of agents, but also the potential for enhanced muscle catabolism, hyperglycemia, hypernatremia, and acquired immunodeficiency adverse drug effects. Muscle catabolism can be associated with diffuse muscular weakness including the diaphragm with associated prolonged duration of mechanical ventilation weaning and PICU duration of stay. Hyperglycemia has been associated with a variety of adverse outcomes in critically ill children, and it is not clear that correction of hyperglycemia with titrated insulin infusions, improves these poor outcomes. Pediatric gene expression data indicate that corticosteroid therapy facilitates additional repression of adaptive immunity beyond that already present in children with sepsis. ⁶⁵-⁶⁶ It makes little sense to augment an existing compensatory anti-inflammatory inflammatory response in septic children who exhibit such a gene expression signature.⁶⁷ Such findings may explain the long standing disconnect regarding corticosteroid therapy for pediatric septic shock: On the one hand corticosteroid administration appears to shorten the duration of septic shock. On the other hand, as noted above, this intervention has not resulted in improved patient-centered outcomes for children with septic shock, perhaps because corticosteroid therapy impairs clearance of the index infection, increases the risk of hospital-acquired infection⁶⁸ or facilitates reactivation of latent viral infections.

Publication and discussion of the APROCCHSS (Activated PROtein C and Corticosteroids for Human Septic Shock and ADRENAL (ADjunctive corticosteroid tREatment iN criticAlly iiL patients with septic shock) randomized controlled trials of adjunctive hydrocortisone for adult septic shock should provide additional key data in terms of providing an evidence-basis for clinical practice in this area. One recent study suggests that a large randomized controlled trial examining early use of corticosteroids in pediatric septic shock is feasible. However, the frequent off protocol administration of empiric corticosteroids in otherwise eligible patients remains a significant challenge. Knowledge translation activities, targeted recruitment, and alternative study designs are possible strategies to mitigate this challenge.⁶⁹ Meanwhile, pediatric critical care providers, collectively and individually at the bedside should be intellectually honest and support quality research that attempts to establish evidence-based medicine for the application of adjunctive corticosteroids for pediatric critical illness.⁷⁰-⁷¹
Conclusion

Adrenal dysfunction is common in critical care settings. CIRCI is a complex and frequent disorder, about which our understanding continues to evolve. The use of corticotropin stimulation testing to diagnose CIRCI remains controversial and its routine use is not recommended to identify the subset of patients with septic shock who should receive hydrocortisone therapy. Currently, treatment with moderate-dose corticosteroids is recommended for children with septic shock who have responded poorly to volume resuscitation and vasoactive-inotrop support and for the patients with early severe ARDS. However, for critically ill children, quality evidence on which to base such recommendations is lacking. In the spirit of a learning health care environment, bedside pediatric critical care clinicians will support well designed interventional interventional trials that will generate evidence for best practice regarding adjunctive corticosteroid treatment.

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References:
