Critical Illness-Related Corticosteroid Insufficiency in Children

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Key Words

Adrenal insufficiency · Critical illness · Septic shock · Children

Abstract

Adequate adrenocortical function is essential for survival in critical illness. Most critically ill patients display elevated plasma cortisol concentrations, which reflects activation of the hypothalamic-pituitary-adrenal axis and is considered to be a homeostatic adaptation. However, many critically ill patients have 'relative' or 'functional' adrenal insufficiency, which is characterized by an inadequate production of cortisol in relation to an increased demand during periods of severe stress. Recently, the term 'critical illness-related corticosteroid insufficiency' (CIRCI) was coined. CIRCI occurs as a result of a decrease in adrenal steroid production or tissue resistance to glucocorticoids. An international task force of the American College of Critical Care Medicine issued recommendations for the diagnosis and management of this condition in adult patients. We review the prevalence, diagnosis, and therapeutic approach to adrenal insufficiency in critically ill children. We found a lack of consensus within the pediatric field as to the optimal approach to CIRCI, and call for an international task force to establish unified guidelines.

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Introduction

During severe illness and stress, the activity of the hypothalamic-pituitary-adrenal (HPA) axis is generally enhanced, and release of cortisol from the adrenal cortex is stimulated [1, 2]. However, in many critically ill patients, this means of adaptation to illness and maintenance of homeostasis may be impaired [3, 4]. The reported prevalence rates of adrenal insufficiency (AI) in critically ill patients vary according to the characteristics of the study population and the diagnostic criteria used. Nevertheless, rates as high as 60–90% have been documented in patients with septic shock [5, 6]. The mechanism leading to dysfunction of the HPA axis during illness are complex and poorly understood. A subset of patients may have structural damage to the adrenal gland from either hemorrhage or infarction [7, 8], which may result in long-term adrenal dysfunction. However, many critically ill patients develop reversible failure of the HPA axis without any structural damage to either the adrenal gland or the pituitary or hypothalamus.

Despite the high prevalence of AI in critically ill patients, the diagnosis and management of this condition remain controversial. In 2008, a consensus statement for recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients was published [9]. For the pediatric population, agreement is low among intensive care and endocrinology specialists regarding diagnostic criteria and the prevalence of

Fig. 1. Activation of the HPA axis during stress. CIRCI may arise due to dysfunction at any point in the pathway. GC-R = Glucocorticoid receptor.

AI associated with critical illness [10]. Pediatric endocrinologists are often required to provide consultation regarding suspected AI in critically ill children. If not promptly diagnosed and treated, this condition may be fatal. The objective of the current article is to review the literature on AI among critically ill children.

The HPA Axis during Acute Illness

Exposure to stressors, such as severe infection, trauma, burns, and surgery, results in a series of coordinated responses that enhance survival. This stress response is mainly mediated by two systems that are functionally related: the sympathoadrenal system and the HPA axis [11]. The sympathoadrenal system includes the sympathetic nervous system and the adrenal medulla. Its activation results in the secretion of epinephrine and norepinephrine from the adrenal medulla. Activation of the HPA axis results in increased secretion of both corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamic paraventricular nucleus. CRH and AVP act synergistically to stimulate the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary [12, 13]. In turn, ACTH stimulates the production of cortisol, adrenal androgens, and, to a lesser extent, mineralocorticoid from the adrenal cortex. Many factors modulate CRH secretion during stress, including adrenergic agonists, opioids, and inflammation cytokines: interleu-

kin (IL)-1, IL-2, IL-6, and tumor necrosis factor- α (TNF- α) [14]. Of note, cytokines, as well as catecholamines, angiotensin II, serotonin, and vasoactive intestinal peptide (VIP), also act directly on the pituitary to stimulate ACTH secretion [15]. In addition, reduction, during stress, of the negative feedback from cortisol to the hypothalamus-pituitary results in increased cortisol concentrations roughly proportional to the severity of the illness [16]. Furthermore, stress also results in decreased secretion of corticosteroid-binding globulin (CBG), leading to an increase in free cortisol concentrations [17]. Finally, the normal circadian rhythm of cortisol secretion, characterized by achievement of the highest concentrations in the morning, is lost during critical illness, as shown by hourly cortisol measurements in critically ill patients [18].

Although severe stress activates the HPA axis, dissociation may occur between plasma ACTH and cortisol concentrations, as demonstrated by suppressed ACTH and elevated cortisol concentrations [19]. A pituitary-independent mechanism was recently suggested for increased cortisol production during critical illness [20]. Possible candidates are cytokines, including IL-6 and TNF- α . Moreover, reduced cortisol breakdown contributed to hypercortisolemia and hence ACTH suppression [20]. Other studies have focused on the tissue and cellular adaptation during stress, including measurement of the tissue cortisol concentration [21] and its activity [22, 23]. The activation of the HPA axis during stress is depicted in figure 1.

Main Actions of Cortisol

During stress, the multiple effects of an increased cortisol concentration contribute to the maintenance of homeostasis. Metabolic effects, especially stimulation of gluconeogenesis and glycogenolysis, increase the availability of energetic substrates. Cardiovascular effects maintain vascular tone, endothelial integrity, and the distribution of fluids within the vascular compartment. Cortisol also potentiates the vasoconstrictor action of catecholamines and decreases the production of nitric oxide. Finally, cortisol counteracts almost every step of the inflammatory cascade modulating the immune response, including a decrease in the production of cytokines and enhancement of the production of macrophage migration inhibitory factor [24].

AI in Critical Illness

Secretory failure of the adrenal gland during critical illness was first described by Waterhouse and Friderichsen in 1911 as caused by bleeding into the adrenal glands resulting from severe bacterial infection (most commonly meningococcus). In the 1940s, Seyle demonstrated that adrenalectomized animals exposed to shock had a high mortality rate, which could be ameliorated by treatment with cortisol [25]. In the early 1980s, the use of etomidate, a hypnotic drug indicated for induction of anesthesia in critically ill trauma patients, was found to be associated with increased mortality [26]. Etomidate blocks the synthesis of cortisol by reversible inhibition of 11- β -hydroxylase. These observations highlight the critical importance of the functional integrity of the HPA axis to survival, particularly in the face of severe insults.

The phrase 'relative AI' describes a state in which activation of the HPA axis occurs, but at an inadequate level to counter the insult. Consequently, the patient may be unable to respond to any additional stress [27]. However, the consensus statement recommends avoiding the term 'relative AI' in the context of critical illness and describing the condition instead as critical illness-related corticosteroid insufficiency (CIRCI) [9]. CIRCI is defined as inadequate corticosteroid activity for the severity of a patient's illness and occurs as a result of a decrease in adrenal steroid production due to dysfunction at any point in the HPA axis or due to tissue resistance to glucocorticoids.

It is important to remember that CIRCI is a dynamic process (i.e. patients who do not have CIRCI at hospital admission may develop it during the course of their illness [28]) and is usually reversible. CIRCI manifests with

insufficient cortisol-mediated downregulation of proinflammatory transcription factors, leading to persistent elevation of proinflammatory mediators over time. It affects the balance between proinflammatory and anti-inflammatory pathways and thereby influences immune, metabolic, vascular, and organ dysfunction.

Mechanism of CIRCI

The mechanism leading to dysfunction of the HPA axis during illness is multifactorial and likely includes decreased production of CRH, ACTH, and cortisol and dysfunction of their receptors. A subset of patients may have structural damage. Necrosis or hemorrhage of the hypothalamus or of the pituitary gland has been reported in sepsis as a result of prolonged hypotension or severe coagulation disorders [29]. Other patients suffer damage to the adrenal gland due to either hemorrhage or infarction [7, 8]. Secondary AI may also follow long-term therapy with exogenous glucocorticoids or other drugs known to decrease cortisol synthesis [30]. However, the reasons for AI in most critically ill patients generally remain unknown.

An inadequate response of the HPA axis to stress can be aggravated by peripheral resistance to glucocorticoids. Different, and probably interacting, mechanisms account for the decreased activity of glucocorticoids. Two of them are a reduction of glucocorticoid receptors [31] and an increase in the conversion of cortisol to inactive cortisone by enhanced activity of 11- β -hydroxysteroid dehydrogenase stimulated by IL-2, IL-4, and IL-13 [15].

Diagnosis of CIRCI in Children

Clinical features of AI include abdominal pain, various mental changes, hyponatremia, hyperkalemia, neutropenia, eosinophilia, and fever. CIRCI is difficult to diagnose on the basis of clinical features alone since many of these signs are not specific and may be due to the critical illness or its treatment. However, hemodynamic instability, dependency on catecholamine therapy despite control of the infection, and occurrence of hypoglycemia should lead to suspicion of CIRCI [24]. To confirm the diagnosis, a random serum cortisol concentration and concentrations at 30 and 60 min after administration of 250 μ g cosyntropin (a synthetic peptide consisting of the first 24 amino acids of ACTH) should be measured. In patients who are not critically ill, an adequate response to the ACTH stimulation test consists of a rise in serum cortisol ≥ 18 μ g/dl (500

Table 1. Summary of published studies on CIRCI in children

First author (year)	Diagnosis	n	Dose of ACTH for stimulation test	Definition of AI	Proportion with AI, %
Hatherill (1999) [56]	septic shock	33	145 µg/m ² to maximum 250 µg	delta cortisol <7 µg/dl	52
Menon (2002) [57]	critical illness	13	<10 kg: 125 µg; >10 kg: 250 µg	basal cortisol <7 µg/dl or poststimulation cortisol <18 µg/dl	31
Bone (2002) [58]	sepsis	42	0.5 µg	basal cortisol <5 µg/dl or poststimulation cortisol <18 µg/dl	17
Pizarro (2005) [59]	septic shock	57	250 µg	basal cortisol <20 µg/dl or delta cortisol <9 µg/dl	18 26
Samransamruajkit (2007) [60]	acute lung injury/ ARDS	16	250 µg	basal cortisol <15.1 µg/dl or delta cortisol <9 µg/dl	25 12.5
Menon (2010) [39]	critical illness	381 202	1 µg on day 1 of admission 1 µg + 250 µg on day 2 of admission	delta cortisol <9 µg/dl delta cortisol <9 µg/dl	30.2 19.8
Hebbar (2011) [40]	SIRS with shock	78	1 µg	basal cortisol <18 µg/dl or delta cortisol <9 µg/dl	56 50 ^a
Hebbar (2012) [6]	critical illness and cancer	20	1 µg	basal cortisol <18 µg/dl or delta cortisol <9 µg/dl	75 50 ^b

ARDS = Acute respiratory distress syndrome; SIRS = systemic inflammatory response syndrome.

^a 88% had either form of AI.

^b 90% had either form of AI.

nmol/l). To increase the sensitivity of the test, a higher cut-off of 20 µg/dl (550 nmol/l) is also used. However, in critically ill patients the definition of an adequate response is different and includes the random cortisol concentration and the *incremental* response (delta cortisol calculated between the baseline cortisol concentration and the highest concentration measured at 30 or 60 min). Many threshold concentrations have been proposed for this definition.

Random Cortisol Concentrations in Critically Ill Patients

For critically ill patients, the proposed concentrations for appropriate random cortisol, measured at any time of the day, range from 10 µg/dl (276 nmol/l) to 34 µg/dl (938 nmol/l) [16]. In the consensus statements for adults, a random total cortisol level <10 µg/dl (276 nmol/l) is recommended as a diagnostic criterion of AI in critical illness [9]. Even though high concentrations of cortisol are a normal adaptation response to stress, concentrations that are too high are predictors of mortality. In a large prospective study, 189 critically ill adult patients were classified based

upon their basal cortisol level and response to the ACTH stimulation test. Mortality was found to be highest in patients with a basal cortisol level >34 µg/dl (938 nmol/l) and a response to the ACTH stimulation test <9 µg/dl (248 nmol/l) [32]. Similarly, a retrospective study of 82 adult patients with septic shock reported that a high basal cortisol and a poor increment on ACTH administration were independent predictors of mortality [33].

ACTH Stimulation Test in Critically Ill Patients

The incremental response after administration of 250 µg cosyntropin has prognostic implications. A small increase from the baseline cortisol concentration to the highest cortisol concentration, measured at 30 or 60 min, has been associated with an increased risk of death [32, 34]. In the consensus statements for adults, a delta cortisol value after ACTH stimulation <9 µg/dl (250 nmol/l) is recommended as a diagnostic criterion for CIRCI. There is still no agreement as to whether this definition is also appropriate for children. A number of definitions have been used in recent years (table 1).

Fig. 2. Decision tree for the investigation and management of adrenal function in critically ill children.

A decision tree for the investigation and management of adrenal function in critically ill children is illustrated in figure 2.

Limitations of CIRCI Diagnosis

Both random cortisol measurement and the ACTH stimulation test have significant limitations in their use with critically ill patients [35]. Assays for serum cortisol measure the total hormone concentration (serum-free cortisol plus the protein-bound fraction). As mentioned above, in most critically ill patients, CBG concentrations

are decreased and the percentage of free cortisol is increased [17]. The dissociation between total and free cortisol is even more marked when serum albumin is <2.5 mg/dl. Although the free cortisol assay has advantages over the total serum cortisol assay, it is not readily available. Moreover, the normal range of free cortisol in critically ill patients is currently not defined. It is likely that improvements in laboratory techniques and increased clinical demands will lead to the availability of the free cortisol assay outside of the context of clinical trials [36, 37].

The ACTH stimulation test also has a number of limitations. Delta cortisol is a measure of the capability of the

adrenal gland to increase the production of cortisol in response to ACTH; it does not assess the integrity of the HPA axis, the response of the axis to other stresses (i.e. hypotension, hypoglycemia), or the adequacy of stress cortisol concentrations. In addition, the ACTH stimulation test may be poorly reproducible, especially in patients with septic shock [38]. Moreover, the delta values employed in published studies should be critically appraised, as increments will differ depending on the baseline cortisol concentrations. In the setting of high basal cortisol concentrations, the cortisol increment has been shown to be reduced in patients with normal adrenal function [3].

According to the consensus statement for adult patients, the 250- μ g ACTH test is currently recommended due to limited data regarding the 1- μ g test [9]. Even though the low-dose test may be more physiologic, it is poorly reproducible, as no pharmacological preparation is available and the 1- μ g solution has to be made up locally. However, in recent studies of critically ill children, the low-dose test was used [6, 39, 40] with 100% sensitivity and 84% specificity (table 1) [39].

Beyond these limitations, the uncertainty in the diagnosis of CIRCI arises from the inability of the current tests to clearly identify the individuals who are truly glucocorticoid deficient at the cellular level [41]. Emerging data suggest that there may be abnormalities in the tissue activity of glucocorticoids in critically ill patients, and that plasma profiles may not be reliable indicators of tissue glucocorticoid activity [21, 22]. Therefore, the decision to treat with corticosteroids should be based on clinical criteria and not on the results of adrenal function testing.

Prevalence of CIRCI in Children

In the absence of established diagnostic criteria for CIRCI in children, the reported prevalence rates vary greatly. Eight pediatric studies using the ACTH stimulation test demonstrated AI prevalence rates between 17 and 90% among critically ill children (table 1). In a large, prospective, multicenter study [39], AI (defined by delta cortisol <9 μ g/dl) was present in 30.2% of critically ill children in variant disease conditions (trauma, sepsis, surgery).

The prevalence of CIRCI in the neonatal population is even more unclear since the normal adrenal response to critical illness has not been fully described for neonates of various gestational ages [4]. A recent study demonstrated

a 56% incidence of AI, defined as a random cortisol level <15 μ g/dl (414 nmol/l), in critically ill term neonates [42]. In premature infants a stimulated cortisol response <18 μ g/dl (497 nmol/l) was measured in about half of critically ill patients [43, 44].

Management

Available clinical studies regarding the outcomes of glucocorticoid use among critically ill patients have generated inconsistent data [45, 46]. According to the consensus recommendations [9], hydrocortisone should be considered in the management strategy of patients with septic shock, particularly in those who have responded poorly to fluid resuscitation and to vasopressor agents, as well as those with early severe acute respiratory distress syndrome. Glucocorticoids restore cardiovascular homeostasis in sepsis through nongenomic and genomic effects, such as by enhancing the responsiveness to catecholamines [47].

The treatment protocol recommended for adults is 50 mg intravenous hydrocortisone every 6 h or a bolus of 100 mg followed by continuous infusion at 10 mg/h. The benefit of hydrocortisone in patients with septic shock has been evaluated in 6 randomized control trials [34, 45, 48–51]. A meta-analysis of these trials demonstrates greater shock reversal on day 7 with hydrocortisone, but no benefit in terms of mortality [9].

Two large randomized control studies, i.e. the French multicenter study [34] and the European multicenter study (CORTICUS) [45], comprised 300 and 500 patients, respectively. The first demonstrated a decrease in mortality and the second did not. A number of factors may account for the difference in results, including bias in the selection of patients, the time window for starting the treatment, treatment doses, and differences in the administration of adjuvant therapy with fludrocortisones. So what should the clinician do? According to the consensus, considering the central role in modulating the stress response and the important cardiovascular effect, the use of hydrocortisone seems rational in adult patients with septic shock who respond poorly to fluid and vasopressor resuscitation [9].

The benefit of additional fludrocortisone is currently unclear. In the French study, 7-day treatment with hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative AI. Since the control group received placebo, it is impossible to isolate the fludrocortisone effect [34]. In the COITSS

study, the addition of fludrocortisones did not result in statistically significant improvement in mortality [52]. Treatment with fludrocortisones is currently considered optional [9].

Regarding pediatric patients, clinical trials examining adjunctive corticosteroid therapy for pediatric critical illness are still meager, and safety and efficacy standards have not been well established [6, 53]. According to the 'clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock' from the American College of Critical Care Medicine, if a child is at risk for absolute AI or pituitary adrenal axis failure, e.g. purpura fulminans, congenital adrenal hyperplasia, prior recent steroid exposure, or hypothalamic/pituitary abnormality, and remains in shock despite epinephrine or norepinephrine infusion, then hydrocortisone should be administered [54]. Recent studies found that 92% of children with CIRCI showed a reduction in vasopressor dosage within 4 h of corticosteroid administration [40], and that the addition of fludrocortisones to the protocol was associated with a shorter duration of norepinephrine support in the septic subgroup [55]. More large randomized trials in children are needed.

Proposed Practical Guidelines for the Critically Ill Child

- CIRCI is frequent during critical illness and is defined as inadequate corticosteroid activity for the severity of a patient's illness. It occurs as the result of a decrease in cortisol production or due to resistance to cortisol.
- Hemodynamic instability, dependency on catecholamine therapy, and hypoglycemia should lead to suspicion of CIRCI.

- In critical illness, a random total cortisol level <10 µg/dl (276 nmol/l) is diagnostic of AI. There is no need to do an ACTH stimulation test. A stress dose of hydrocortisone should be given. A random total cortisol level >34 µg/dl (938 nmol/l) is associated with a poor prognosis.
- When random cortisol ranges from 10 to 34 µg/dl (276–938 nmol/l), a 250-µg ACTH stimulation test should be done.
- A delta cortisol value after ACTH stimulation <9 µg/dl (250 nmol/l) is diagnostic for CIRCI and hydrocortisone therapy.
- It is important to remember that CIRCI is a dynamic process (i.e. patients who do not have CIRCI at hospital admission may develop it during the course of their illness) and is usually reversible.

Conclusions

CIRCI is a common and often underdiagnosed disorder in critically ill patients. Interest in this condition has grown in recent years, mostly among intensive care physicians treating adult patients. Clinical trials examining CIRCI among pediatric critically ill patients are still meager and prevalence rates, diagnostic criteria, and optimal treatment are still controversial. An international task force for the establishment of unified protocols for ACTH testing and for defining AI in the pediatric population is needed.

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