Background: Adrenal insufficiency (AI) is a well-known cause of potentially life-threatening disorders. Defects at each level of the hypothalamic-pituitary-adrenal axis can impair adrenal function, leading to varying degrees of glucocorticoid (GC) deficiency. Iatrogenic AI induced by exogenous GCs is the most common cause of AI. The criteria for the diagnosis and management of iatrogenic AI, neonatal AI, and critical illness-related corticosteroid insufficiency (CIRCI) are not clear.

Data sources: We reviewed the recent original publications and classical data from the literature, as well as the clinical, diagnostic and management strategies of pediatric AI.

Results: Practical points in the diagnosis and management of AI with an emphasis on iatrogenic AI, neonatal AI, and CIRCI are provided. Given the lack of sensitive and practical biochemical tests for diagnosis of subtle AI, GC treatment has to be tailored to highly suggestive clinical symptoms and signs. Treatment of adrenal crisis is well standardized and patients almost invariably respond well to therapy. It is mainly the delay in treatment that is responsible for mortality in adrenal crisis.

Conclusion: Education of patients and health care professionals is mandatory for timely interventions for patients with adrenal crisis.

Key words: adrenal insufficiency; critical illness; hypothalamo-pituitary-adrenal axis; iatrogenic; steroids

Introduction

Adrenal insufficiency (AI) encompasses a wide spectrum of life-threatening disorders related to the congenital or acquired pathologies of the adrenal cortex (primary AI), pituitary gland (secondary AI) or hypothalamus (tertiary AI). The clinical findings of primary AI are associated with deficient synthesis or release of glucocorticoids (GCs) and frequent deficiency of mineralocorticoids.[1-3] Secondary and tertiary AI are associated with deficiencies of adrenocorticotropic hormone (ACTH) and corticotropin releasing hormone (CRH), respectively. Consequently, biochemical findings of mineralocorticoid deficiency are not expected in the latter two subtypes of AI.

Physiology of the adrenal functions

The mature adrenal cortex comprises the zona glomerulosa (outermost layer), zona fasciculata (intermediate zone), and zona reticularis (innermost layer), which are associated with aldosterone, cortisol and androgen synthesis, respectively.

The adrenal cortex is under control of the hypothalomo-pituitary-adrenal (HPA) axis for regulation of cortisol synthesis, which is stimulated by CRH and arginine vasopressin secretion from the hypothalamus and by ACTH secretion from the pituitary gland. Mineralocorticoid synthesis is regulated by the renin-angiotensin-aldosterone system, sympathetic innervation, blood pressure, intravascular volume and extracellular potassium concentrations.

The adrenal medulla is associated with production of catecholamines (adrenaline and noradrenaline), which is regulated by GC synthesis from the neighboring adrenocortical cells. The final step in adrenaline biosynthesis is the methylation of the primary amine of noradrenaline. This reaction is catalyzed by the enzyme phenylethanolamine N-methyltransferase, which is positively regulated by cortisol.[4]

The synthesis of ACTH in the developing foetus begins as early as the seventh week of gestation, and the rate of cortisol production reaches a maximum level in mid-gestation.[4] The placental transfer of cortisol
from the mother to the fetus is negligible from the second trimester because of the inactivation of cortisol to cortisone transformation via the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD 2).

The synthesis of cortisol from cholesterol requires the sequential action of several enzymes and cofactors (Fig. 1). The secretion of cortisol has a diurnal rhythm, which is established in the first months of life; with a daily endogenous secretion rate of 6-10 mg/m² per day. Seventy-five percent of plasma cortisol is bound to corticosteroid binding globulin (CBG) and 15% to albumin. The remaining is unbound; this free fraction (10%) constitutes the physiologically active form of cortisol. Plasma cortisol is metabolized primarily in the liver by the cytochrome P450 enzyme system, and excreted via urine and feces.

Owing to the pre- and post-natal physiologic changes in its secretion and the acquisition of the circadian rhythm after the first month of life, normal plasma cortisol levels change with age and the time of the day (Table 1).

Despite adrenal physiology and the synthesis of cortisol used in replacement therapy being well-defined in 1949, the diagnosis and management of AI may still be challenging.

**Etiology**

Unlike tuberculosis and autoimmune adrenalitis (AIA), which are far more prevalent in adults, primary AI is more commonly associated with genetic disorders. Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is the most frequent cause of primary AI, followed by other genetic causes and AIA (Table 2). Al though primary AI is more common in girls, but adrenoleukodystrophy and dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1 (DAX1) defect-related AI occurs more commonly in boys because of X-linked transmission. The occurrence of acquired primary AI may be due to the local trauma and bilateral adrenal hemorrhage induced by perinatal stress in newborns and acute infections in childhood and adolescence. Primary AI may also be due to anti-phospholipid antibody syndrome in the context of connective tissue diseases in adolescents and adults. While tuberculosis was the major cause in the first half of the preceding century, AIA, fungal infections, and HIV began to dominate in the last decade.

Other causes of AI include congenital or acquired hypopituitarism and ACTH unresponsiveness. ACTH unresponsiveness may be isolated as familial GC deficiency (FGD), or it may be associated with achalasia and alacrima (Triple A syndrome) (Table 2).

Novel genes involved in detoxification of mitochondrial reactive oxygen species have recently been implicated in FGD. Meimaridou et al identified mutations in the nicotinamide nucleotide transhydrogenase (NNT) gene in patients with pure FGD, and Prasad et al found a mutation in thioreredox reductase 2 in a consanguineous family that presented with FGD. Mutations were recently described in the minichromosome maintenance-deficient 4 homologue gene in Irish patients with short stature, chromosomal breakage, immune deficiency and progressive AI characterized by ACTH resistance with GC deficiency and normal mineralocorticoid levels.

**Table 1. Age related normal values of random serum cortisol in humans**

<table>
<thead>
<tr>
<th>Age</th>
<th>Time</th>
<th>Range (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>-</td>
<td>27.6-303.5</td>
</tr>
<tr>
<td>26-28 GW, Day 4</td>
<td>-</td>
<td>69.0-251.0</td>
</tr>
<tr>
<td>Term</td>
<td>-</td>
<td>322.8-386.1</td>
</tr>
<tr>
<td>Day 3</td>
<td>-</td>
<td>55.2-303.4</td>
</tr>
<tr>
<td>Day 31-11 mon</td>
<td>-</td>
<td>77.2-634.3</td>
</tr>
<tr>
<td>Day 7</td>
<td>-</td>
<td>Not determined</td>
</tr>
<tr>
<td>Day 12 mon-15 y</td>
<td>08:00 am</td>
<td>82.6-578.3</td>
</tr>
<tr>
<td>Adults</td>
<td>16:00 pm</td>
<td>220.3-523.3</td>
</tr>
</tbody>
</table>

Modified with permission from Esotex inc. GW: gestational weeks. **: none.
Isolated ACTH deficiency

Granulomatous disorders (sarcoidosis)

Cranial irradiation

Hypothalamic tumors

Hypopituitarism

PROP1

Exogenous glucocorticoid intake

Familial hypercholesterolemia

LDLR

MTP

Abeta-lipoproteinemia

DHCR7

Smith-Lemli-Opitz disease

ABCD1

FAZ2

X-linked adrenoleukodystrophy

Neonatal adrenoleukodystrophy

Kearns-Sayre syndrome

Familial glucocorticoid deficiency

DNA repair defect

Allgrove Syndrome (triple A)

Deficiency of mitochondrial radicals’ detoxification

Wolman disease

Smith-Lemli-Opitz disease

Abeta-lipoproteinemia

Familial hypercholesterolemia

Exogenous glucocorticoid intake

Hypopituitarism

Hypothalamic tumors

Cranial irradiation

Granulomatous disorders (sarcoiôdis)

Isolated ACTH deficiency

Iatrogenic AI is usually caused by long-term administration of GCs, and is the most common form of AI.\(^{[44]}\) Suppression of the HPA might be caused by administration of pharmacologic doses of GCs for more than 2-3 weeks. The suppression may be subclinical, or may be sufficiently severe to cause acute adrenal crisis. Megestrol acetate, an orexigenic medication with GC properties, has also been associated with iatrogenic adrenal insufficiency.\(^{[33]}\) The list of drugs associated with iatrogenic AI is not exhaustive and includes many drugs such as ketoconazole, etomadone, and mitotane.

The term critical illness-related corticosteroid insufficiency (CIRCI) has recently been coined to describe patients with critical illness who are not able to mount a cortisol response, which is expected given the severity of illness.\(^{[34,35]}\)

**Epidemiology of AI**

A retrospective study from the United States of America suggested that the prevalence of AI in childhood was higher than expected, almost equal to that of CAH, which occurs in approximately 1 per 10 000 to 18 000 infants.\(^{[36]}\) A study from Italy provided an estimated 117 cases per million people.\(^{[37]}\)

**Clinical symptoms and signs**

The signs and symptoms of AI are summarized in Table 3. The clinical spectrum of AI ranges from insidious, nonspecific complaints such as fatigue and weakness to full-blown acute vascular collapse due to hypovolemic shock. In the neonatal period and...
The clinical manifestations of patients with secondary or tertiary AI are similar to those of patients with primary AI but less severe and without salt wasting because aldosterone is regulated mainly via the renin-aldosterone system and is only partially dependent on ACTH. Skin hyperpigmentation is not present, and ACTH deficiency is often associated with other anterior pituitary hormone deficiencies. Therefore, multiple pituitary hormone deficiency-related findings such as hypothyroidism and short stature may predominate when AI is due to ACTH deficiency.

### Diagnosis of adrenal insufficiency

There is a continuing debate in the pediatric literature over the diagnostic criteria of AI. Further, the concept of normal basal adrenal function with inability to mount a stress reaction (i.e. relative AI) is being called into question.

Inappropriately low cortisol levels allow for the biochemical diagnosis of AI. Basal cortisol and ACTH levels may be diagnostic under stress conditions that present as adrenal crisis. Blood samples must be obtained prior to initiation of GC therapy to prevent falsely low ACTH levels. Patients at risk of AI may have considerably overlapping 8 o’clock cortisol levels in the morning when compared with those of normal healthy individuals. Plasma 8 o’clock cortisol level <138 nmol/L (5 μg/dL) or salivary cortisol <5 nmol/L (0.18 μg/dL) is very suspicious for AI, and plasma 8 o’clock cortisol level >550 nmol/L (20 μg/dL) or salivary cortisol >160 nmol/L (5.8 μg/dL) essentially rules out AI in patients without stress. Markedly elevated ACTH (>200 pmol/L (910 pg/mL)) and very low cortisol levels are diagnostic for primary AI. Dynamic tests of the HPA axis are usually necessary to increase the diagnostic sensitivity and specificity of the routine biochemical tools (Table 4).

### ACTH stimulation test

In primary and secondary AI, acute stimulation with IV ACTH will not result in an adequate cortisol response of the adrenals. In secondary AI, atrophy of the adrenal cortex due to lack of trophic stimulation by ACTH results in reduced cortisol response, similar to the inadequate tissue response in primary AI. A variety of different doses and durations have been described with assay-specific reference values. In clinical practice, short infusion tests are usually sufficient. The standard 250 μg/m² ACTH test relies on the peak cortisol level at 30 and 60 minutes of blood sampling following an IV injection of ACTH. The definition of sufficient response tends to vary due to different assays or different criteria.
Generally, peak cortisol is expected to exceed 500-550 nmol/L (18 to 20 μg/dL). Normal cortisol response is also defined by a 2- to 3-fold rise in cortisol levels or by an absolute increase of 193 nmol/L (7 μg/dL). The test can be performed at anytime during the day. It is limited by its poor sensitivity and high rate of false positivity in the setting of secondary AI, where atrophy of the adrenal cortex is partial, which allows some response to ACTH. The low dose (1 μg or 0.5 μg/m²) ACTH test is practised in the latter setting with post-ACTH cortisol levels measured at 30 minutes. Generally, a plasma cortisol peak level >500-550 μg/dL (18-20 μg/dL) is considered a normal response. The low dose ACTH test cannot differentiate tertiary from secondary AI, thus requiring additional tests. The low-dose ACTH test should be performed in the morning, with cosyntropin administered intravenously through short tubing. Notably, ACTH has to be drawn out of a 250-μg vial for dosing because ACTH adheres to glass and plastic and is unstable in solution; therefore, issues with dosing accuracy may lead to low test specificity. The results of meta analyses that evaluated the sensitivity of the 1 μg- vs. 250 μg ACTH tests were contradictory.

The low-dose corticotropin stimulation test is superior to the standard-dose test for the diagnosis of central AI in children. Due to the lack of cortisol assay standardization and other reasons for measurement variability, the error in measuring cortisol can be up to 165 nmol/L (6 μg/dL). Thus caution should be taken when making clinical decisions based on cortisol values close to threshold values. In addition to the high variability in the cortisol diagnostic thresholds, especially in the exclusion of secondary/ tertiary AI, a low likelihood of AI does not exclude the possibility of future AI, especially after progression of hypothalamic-pituitary disease or radiation therapy. Hence, longitudinal assessments may be required. The low-dose corticotropin stimulation test has not been validated in patients with acute illnesses, abnormal sleep-wake cycles, or acute hypothalamic-pituitary disorders (e.g. within 1 month of pituitary surgery). Low-dose testing should be performed by personnel knowledgeable of the multiple steps required for preparation and administration. If the quality of administering a 1-μg dose of corticotropin is doubted, administration of the standard dose of 250 μg (reconstituted with 1 ml of sterile diluent) and subsequent measurement of serum cortisol 30 minutes after intravenous injection is highly recommended. A result less than 440 nmol/L (16 μg/dL), which is the same threshold used for low-dose testing, strongly suggests hypothalamic-pituitary AI. Children with a mature HPA axis (typically older than 3 years) may achieve the maximal total daily ACTH production rates, which can reach 250 μg. Using corticotropin analog in a 1-μg dose without body surface adjustment is logical and feasible given the technical difficulties diluting and administering available corticotropin formulations in

### Table 4. Dynamic tests evaluating the hypothalamo-pituitary-adrenal axis

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Procedure</th>
<th>Mechanism of action</th>
<th>Interpretation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard (250 μg/m²)- corticotropin (ACTH)</strong></td>
<td>Measure plasma cortisol levels at 30 and 60 min following IV 250 μg- ACTH</td>
<td>ACTH induces an increase in cortisol secretion from the adrenals</td>
<td>Peak plasma cortisol &gt;500-550 μmol/L (18-20 μg/dL) or an absolute increase in cortisol of 193 nmol/L (7 μg/dL) is expected</td>
<td>Diagnostic for primary AI. Can be performed anytime during the day. Should not be performed in suspected secondary AI issues with dosing accuracy. Cannot differentiate secondary vs. tertiary AI</td>
</tr>
<tr>
<td><strong>Low dose (1 μg or 0.5 μg/m²)- ACTH</strong></td>
<td>Measure plasma cortisol levels at 30 and 60 min following IV 1 μg- ACTH</td>
<td>Same as above</td>
<td>Peak plasma cortisol &gt;500-550 μmol/L (18-20 μg/dL) is expected</td>
<td></td>
</tr>
<tr>
<td><strong>Metyrapone</strong></td>
<td>Measure ACTH, cortisol, and 11-deoxycorticosterone (11-DOC) at 08:00 am after a single midnight metyrapone dose of 30 mg/kg (max: 3 g)</td>
<td>Metyrapone inhibits 11β-hydroxylase. A decrease in cortisol leads to a subsequent rise in ACTH and CRH levels</td>
<td>Plasma 11-DOC &gt;210 nmol/L (7 ng/dL) is expected.</td>
<td>May induce adrenal crisis in at-risk patients. False positive results in patients receiving glucocorticoids. 4% of the population have increased clearance of metyrapone, which can also be induced by drugs such as phenytoin, rifampin</td>
</tr>
<tr>
<td><strong>Insulin hypoglycemia</strong></td>
<td>Measure glucose and cortisol levels at baseline and q15 min up to 90-120 min after IV insulin (0.05-0.15 U/kg body weight)</td>
<td>Hypoglycemia activates the hypothalamic-hypophysial axis and induces corticotropin releasing hormone, ACTH and cortisol secretion.</td>
<td>Peak plasma cortisol &gt;500-550 μmol/L (18-20 μg/dL) is the normal response</td>
<td>Considered as &quot;gold standard&quot; by some authors. Safety issues limit its use. Contraindicated in heart disease, seizures and cerebrovascular disease</td>
</tr>
<tr>
<td><strong>Glucagon</strong></td>
<td>Measure cortisol at baseline and q30 min up to 180 min after intramuscular glucagon 0.1 mg/kg (max: 1 mg)</td>
<td>Glucagon stimulates ACTH secretion and therefore cortisol.</td>
<td>Peak plasma cortisol &gt;500-550 μmol/L (18-20 μg/dL) is the normal response</td>
<td>A safer alternative to insulin hypoglycemia test</td>
</tr>
<tr>
<td><strong>CRH</strong></td>
<td>Measure ACTH and cortisol at baseline and q15 min over 60-120 min post-CRH injection (1 μg/kg, max: 100 μg)</td>
<td>CRH induces the hypophysia to secrete ACTH and therefore cortisol.</td>
<td>An increase in ACTH by &gt;34% and in cortisol by &gt;20% is the normal response</td>
<td>Other definitions of normal response to the test exist. Closely correlates with the insulin hypoglycemia test, with a much better safety profile</td>
</tr>
</tbody>
</table>

CRH: corticotropin releasing hormone; ACTH: adrenocorticotropic hormone; IV: intravenously; AI: adrenal insufficiency.
doses even lower than 1 μg. Low-dose corticotropin analogue testing in children younger than 3 years has not been well studied.\(^\text{[46,47]}\) DHEAS blood levels might also be helpful in assessing the HPA axis, particularly when the results of the low-dose stimulation test are close to either of the two threshold values.\(^\text{[46,47]}\)

**Metyrapone test**

Metyrapone inhibits the enzyme 11-β-hydroxylase, thereby inhibiting the conversion of 11-deoxycortisol (11-DOC) to cortisol. This results in a decrease in cortisol, and subsequent rise in ACTH and CRH levels in accordance with the release of feedback inhibition in healthy individuals with an intact HPA axis. The overnight single dose test is the most commonly practised protocol as described by others.\(^\text{[43]}\) The test relies on the measurement of ACTH, cortisol and 11-DOC at 8 o’clock in the morning after a single midnight metyrapone dose of 30 mg/kg (maximum 3 g). If morning serum cortisol is <138 nmol/L (5 μg/dL), blockade is considered sufficient. Plasma 11-DOC levels >210 nmol/L (7 ng/dL) suggest an intact HPA axis. Measurement of ACTH is useful to distinguish primary from secondary AI, with normal ACTH response being >340 pmol/L (75 pg/mL). Because this test is associated with a risk of inducing adrenal crisis in at-risk patients, occasionally even in healthy individuals, it is unsafe in the outpatient setting. Additionally, false positive results may be observed in patients receiving GCs such as dexamethasone. Clearance of metyrapone shows inter-individual variability, with 4% of people being fast metabolizers. Moreover, clearance of metyrapone can be induced by several drugs such as phenytoin and rifampicin.\(^\text{[43,48]}\)

**Insulin-induced hypoglycemia test**

A normal response to hypoglycemia requires an intact HPA axis because it is a potent stimulant for CRH, and therefore of ACTH and cortisol. This test is done in the inpatient setting and requires bed rest and an overnight fast, with an intravenous catheter inserted.\(^\text{[43]}\) Hypoglycemia <2.2 mmol/L (40 mg/dL) is induced by administering insulin at a dose of 0.05-0.15 U/kg body weight. Blood samples for glucose and cortisol are obtained at baseline, and every 15 minutes up to 90-120 minutes post-insulin injection. Hypoglycemia symptoms such as sweating and tremor indicate an effective challenge. Peak cortisol levels are usually observed when blood glucose level is less than 40 mg/dL. Frequent blood glucose measurements are needed to verify the target glucose level of less than 40 mg/dL. The test should result in a peak cortisol level >500-550 nmol/L (18-20 μg/dL).\(^\text{[43,48]}\) This test is regarded as the gold standard for the assessment of AI because it also allows simultaneous assessment of ACTH and growth hormone reserves. Yet, safety concerns limit its use even in tertiary care centers. It is contraindicated in heart disease, seizure-related disorders and cerebrovascular disease.

**Glucagon stimulation test**

The glucagon stimulation test is a feasible alternative to the insulin-induced hypoglycemia test in the evaluation of central AI. This test relies on the stimulatory effect of glucagon on ACTH secretion and therefore of cortisol. Plasma cortisol levels are measured every 30 minutes up to 180 minutes following intramuscular injection of glucagon 0.1 mg/kg (maximum 1 mg). Normal response is defined as peak plasma cortisol >500-550 nmol/L (18-20 μg/dL).

**CRH stimulation test**

The ovine or human CRH (the ovine form is preferred owing to higher bioavailability) test assesses the ability of the pituitary gland to secrete ACTH for stimulation of cortisol secretion. This test closely correlates with the insulin hypoglycemia test from a diagnostic perspective, but it has fewer adverse effects. CRH is given as an intravenous bolus of 1 μg/kg (maximum 100 μg) at 8 o’clock following overnight fast. Plasma cortisol and ACTH levels are measured at 15 minutes intervals over 60 to 120 minutes following injection of CRH. Plasma ACTH peaks within 15 to 30 minutes and cortisol peaks around 30 to 60 minutes after injection. Patients with secondary AI will not have sufficient ACTH and cortisol secretion. However, patients with tertiary AI will have a prolonged ACTH response and a subnormal cortisol response. Owing to the differences in reported reference values, normal values should be determined by individual laboratories. An increase in ACTH by >34% and in cortisol by >20% is interpreted as the normal response;\(^\text{[49]}\) although other definitions of normal response do exist.

**Tests determining the etiology of adrenal insufficiency**

Specific enzyme deficiency in the adrenal steroid biosynthetic pathway (Fig. 1) will result in accumulation of precursors and loss of product(s) of the related enzymatic step. A thorough description of the precursors necessary to diagnose and treat these enzymatic disorders of steroidogenesis is beyond the scope of this review, and the reader is referred to textbooks of pediatric endocrinology for further information.

Adrenal androgens play a less important role in the diagnosis of primary AI. Androgens are generally low,
except for some cases of CAH. After adrenarche and puberty, adrenal androgens comprise about half of the circulating androgen pool in women. Therefore, adrenal androgen deficiency may not necessarily be an issue of childhood.

Additional diagnostic tests
The diagnosis of AIA is largely based on the presence of circulating antibodies directed against adrenal cells or their cellular contents such as 21 hydroxylase, 17 hydroxylase, 11 hydroxylase or microsomes.

The diagnosis of adrenoleukodystrophy in the male patient with isolated AI requires assessment of very long chain fatty acid (VLCFA) levels, which are elevated due to impaired β-oxidation in peroxisomes. Genotyping for ABCD1 gene mutation should be performed to confirm the diagnosis in proband and family members for genetic counseling.

Patients with congenital lipoid CAH or congenital adrenal hypoplasia due to steroidogenic factor-1 mutations may have 46 XY sex reversal. Thus, karyotype is suggested in such cases even in the absence of ambiguous genitalia.

The presence of lactic acidosis, myopathy or sensorineural deafness suggests mitochondrial disease such as Kearns-Sayre syndrome. Wolman disease and Smith-Lemli Opitz (SLO) may be suspected by characteristic physical findings and warrant specific biochemical and genetic tests. Whenever feasible, confirmation of suspected genetic disorders of the adrenal cortex should include genetic analysis of candidate genes.

Prenatal diagnosis is available for some of the heritable causes of AI. If a familial mutation is known, such as in CAH, FGD, or Allgrove syndrome, prenatal genetic testing should be performed. Adrenoleukodystrophy can be diagnosed by VLCA levels in cultured amniocytes and chorion villus cells. Screening for SLO syndrome can be done by prenatal ultrasound or by genetic or enzymatic analysis. Of the congenital anomalies associated with SLO syndrome, 80% are diagnosed using ultrasound in-utero. A prenatal ultrasound that shows nonvascular intrauterine growth retardation plus another congenital anomaly should raise the suspicion of SLO syndrome.

Special diagnostic considerations
Iatrogenic adrenal insufficiency due to glucocorticoid use
Pharmacologic doses of GCs are well known to induce HPA axis suppression. As yet there are no uniform guidelines to assess GC-exposed patients with respect to AI, and their management differs due to a) routes of administration of GCs; b) duration of exposure to GCs; c) inter-individual susceptibility to GC-induced suppression of the HPA axis due to GC receptor gene mutations or polymorphisms, alterations in signal transduction mechanisms; d) variability in dosing, and e) diverse etiologies that necessitate GC use.

When patients are unable to tolerate withdrawal of a GC, in the absence of an acute relapse of the underlying disease and in the absence of HPA axis suppression, they are diagnosed as having withdrawal syndrome. The clinical presentation is characterized by physical and psychological dependence. Physical dependence is characterized by the classic signs and symptoms of AI (Table 2). Psychological dependence mostly manifests as mood swings and emotional lability, although delirium and psychotic states may also occur. The syndrome can occur even when the patient is receiving supraphysiologic doses of GCs.

In general, AI is not expected with short-term use of GCs, even with high potency GCs like dexamethasone at pharmacologic doses, for a period of 7-14 days. However, the use of steroids for longer than 2-3 weeks' duration should alert the clinician to the emergence of occult or manifest AI if abrupt cessation of the medication is practised. In adults, as little as 2 weeks of high-dose GC use may result in suppression of endogenous cortisol production for up to 1 year. In children treated for leukemia, a 4-week course of GCs may suppress the HPA axis for up to 8 weeks after cessation of therapy. Moreover, suppression of the axis cannot be reliably predicted by neither the dose nor the duration of therapy.

Administration of GCs by parenteral or oral route apparently results in greater bioavailability than nasal, topical or inhalant routes. However, chronic administration of nasal/inhalant GCs to patients with allergic rhinitis or asthma may induce subtle AI. Zöllner et al documented HPA suppression using the metyrapone test in about two thirds of asthmatic children who showed good adherence to inhalant/nasal GC therapy. They documented overt hypocortisolism, hypothalamo-pituitary suppression and HPA suppression in 6.1%, 22.9%, and 16.1% of children with asthma, respectively. Presence of HPA suppression was predicted using concomitant use of nasal GC, body mass index (BMI) (with lower BMI increasing the risk of AI) and good adherence to therapy. There is insufficient evidence to justify routine use of the metyrapone test in all patients with asthma prior to initiation of GCs and on follow-up because the pros of administering GCs seem to surpass the risk of HPA suppression, and metyrapone use is related to vomiting and adrenal crisis.

Morning ACTH measurements have low diagnostic
yield for assessing AI because the precision of these assays is limited for low values and the morning ACTH levels are lower in children than in adults (5-20 pg/mL vs. 20-80 pg/mL), which makes it difficult to differentiate between normal low values and true suppression of the HPA axis. Baseline serum 8 o'clock cortisol levels lower than 83-138 nmol/L (3-5 μg/dL) suggests AI, and levels greater than 550 nmol/L (20 μg/dL) indicate normal adrenal function. Basal ACTH and cortisol values are of use only if the results are at the extremes of normal. Intermediate values require dynamic tests to be done to evaluate the HPA function. Physiologic factors such as puberty, exercise, and changes in CBG concentration can also influence the cortisol values. With the exception of dexamethasone, cortisol assays should be performed at least 24-48 hours after cessation of GC therapy because they cross-react with the cortisol metabolites.

If it is not desirable to discontinue GC treatment as is the case in several hematologic diseases such as chronic immune thrombocytopenic purpura, leukemia, or if the patient has not been receiving GC therapy for a sufficiently long period, the CRH test may be very helpful to evaluate ACTH and cortisol responses. In the latter setting, low-dose ACTH may yield a normal result with good cortisol response when direct stimulation of a not-yet atrophied adrenal cortex could be expected. However, if ACTH secretion is compromised, CRH testing may yield a subnormal rise in endogenous ACTH. The CRH test is also reliable for detecting HPA suppression in preterm infants who have been exposed to dexamethasone in utero, initially administered to their mothers to enhance fetal lung development.

If performance of dynamic tests to assess adrenal function is not possible, patients on GCs for prolonged periods can be considered at risk of AI up to 12 months after withdrawal.

Assessment for adrenal insufficiency in the newborn

In preterm neonates, de novo cortisol synthesis begins at 30 gestational weeks (GW) owing to insufficiency of 3-β-hydroxysteroid dehydrogenase activity. Placental progesterone is used in cortisol synthesis prior to 30 GW. Moreover, relative 11-β-hydroxysteroid dehydrogenase type 2 (11-β-HSD2) deficiency of the preterm placenta allows placental passage of maternal cortisol to the fetus, thereby suppressing endogenous foetal cortisol synthesis.

In term neonates, abrupt withdrawal of placental transfer of CRH induces transient blunting of the hypophyseal ACTH secretion to maintain cortisol production. This physiologic condition may be tolerated by healthy newborns but may be detrimental for the sick neonate.

Although the liability of the newborn to relative AI is well documented, different biochemical parameters with different cut-off levels have been suggested to be diagnostic for neonatal AI. Basal cortisol >414 nmol/L (15 μg/dL), peak cortisol response to low-dose ACTH test >500 nmol/L (18 μg/dL), or a difference in baseline and peak cortisol levels >248 nmol/L (9 μg/dL) or >12% have been suggested to rule out AI in the newborn. However, correlations between the suggested cut-off values and clinical diagnosis have not been conclusively demonstrated. The presence of hemodynamic compromise, vigorous need of electrolyte resuscitation or vasopressor resistant hypotension suggest neonatal AI.

Critical illness-related corticosteroid insufficiency (CIRCI)

Relative AI is an enigmatic entity that has been a subject of much debate in the literature. It refers to a normal basal cortisol with insufficient stress cortisol level (either by the ACTH test or by random cortisol during stress). Attempting to determine the prevalence of abnormal corticotropin test in critical illness is complicated by the use of different end-points and different populations, although the majority of work has been carried out in patients with sepsis and septic shock. The inconsistent results reported in several trials regarding the relationship between cortisol response to ACTH and illness severity in critical illness may be due to varying time points of assessment, use of different assays, and pharmacologic confounders.

Critically ill adults with a normal baseline serum cortisol but inappropriately low response to acute stimulation demonstrated improved survival when treated with stress doses of hydrocortisone (HC), although these findings have not been replicated.

CIRCI refers to inability of the adrenal cortex to mount an appropriate response to the patient's critical condition. It may occur due to reduced cortisol production or to resistance to cortisol action. Hemodynamic instability and vasopressor treatment dependency are strong indicators of CIRCI. A random total serum cortisol level <276 nmol/L (10 μg/dL) in a critically ill child indicates AI and the standard ACTH (250 μg) test is not necessary. If serum cortisol ranges between 276-938 nmol/L (10-34 μg/dL), the 250 μg-ACTH test should be performed, and if the delta cortisol value is <248 nmol/L (9 μg/dL), then the diagnosis of CIRCI is confirmed, which supports the initiation of therapy.

The response to ACTH is assessed by measurement
of total plasma cortisol rather than separate evaluation of the protein bound and free cortisol. Approximately 95% of circulating cortisol is bound to CBG. However, it is the free fraction in plasma that exerts a biologic effect. In acute illness, CBG and albumin levels may decline rapidly, which results in higher plasma free cortisol rather than total cortisol. Therefore, there is a sound pathophysiologic basis to consider measuring free cortisol rather than total cortisol. Nevertheless, this was not conclusively demonstrated in several studies. \[86,84\] In addition, the methods used to separate unbound and bound fractions prior to measurement are cumbersome and labor intensive. Even small variations in temperature markedly influence free cortisol in plasma. 

Significant fluctuations in total cortisol in plasma were demonstrated by Venkatesh et al.,\[87\] who demonstrated that maximal spontaneous hourly rises in plasma cortisol exceeded those induced by ACTH thus raising question marks about the validity of the ACTH test. An important determination of the cortisol output by the adrenal cortex is the ACTH presentation rate to the zona fasciculata, which in turn, is influenced by adrenal blood flow. The final measurement of plasma cortisol following ACTH is not merely dependent upon the plasma ACTH concentration and the responsiveness of the fasciculata cells but is significantly influenced by other factors such as cardiac output and adrenal blood flow. Current tests are unable to clearly identify who is truly GC deficient at the cellular level and who requires GC supplementation. The available evidence does not support the use of the ACTH test in the setting of acute critical illness to assess adenocortical function nor should it be used to guide steroid therapy in this setting.\[88\]

A recent study by Balbao et al.\[89\] provided a comparative evaluation of adrenal function in critically ill children with 250 μg ACTH test vs. healthy peers, and assessed the associations of biochemical and clinical scores related to the severity of illness. They did not find the delta serum cortisol response to be related to the outcome, but salivary cortisol, which is highly correlated with free cortisol levels in the circulation, was shown to be indicative of the need for vasoactive or inotropic support when it is ≤226 nmol/L (8.2 μg/dL). However, the sensitivity and specificity of the test at this cut-off point were only 79% and 62%, respectively.

The decision to treat a critically ill patient with GCs must be made on a case-by-case basis until further definitive evidence is available.

Management of adrenal insufficiency

Acute adrenal crisis

The treatment of adrenal crisis involves urgent correction of the dehydration secondary to GC and mineralocorticoid deficiency. Fluid and electrolyte resuscitation by IV 0.9% NaCl at a dose of 20 mL/kg in one hour helps expand the effective blood volume, and corrects hypotension. Subsequent fluid administration includes deficit, on-going losses and maintenance fluids. Half of the calculated fluid is given in 8 hours, and the remaining half in 16 hours. The potassium concentration usually remains elevated, and the acidosis may persist.\[88\] If hyperkalemia is associated with electrocardiographic changes, it may be necessary to use a sodium-potassium exchange resin such as sodium-polyacrylate. Insulin and glucose (0.1 U/kg and 0.5 g/kg intravenously, respectively, over 30 minutes) may also be given for the reduction of serum potassium levels with careful monitoring of blood glucose levels. Treatment with a GC should be given as an intravenous bolus over several minutes. Several GC preparations could be used for this purpose. In general, the current recommendation is to use HC 25 mg, 50 mg, and 100 mg in patients aged 0 to 3 years, 3 to 12 years and ≥ 12 years, respectively.\[88\] The initial bolus is followed by the same dose given as in continuous infusion or as four doses divided over a 24-hour period. It should be noted that the suggested doses are not evidence-based, and are purely arbitrary. If HC is unavailable, methylprednisolone 10-15 mg/m² per day could be given. Prednisone should not be used in the setting of adrenal crisis because it requires first pass metabolism in the liver to yield active metabolites.

The education of patients and health care professionals is considered to be a key step for crisis prevention. Anecdotal evidence suggests that the management of adrenal crisis is frequently insufficient, which contributes to the mortality rate of the patients. In a recent study by Hahner et al.,\[89\] major deficiencies in the care of adult patients with AI were documented when the target times set by an expert survey regarding the optimal time for access of the patients to medical attention and time to intervention by HC injection were compared with real world data.\[89\] The study showed that the time delay consisted of the time between calling for help and the arrival of the emergency physician or the hospital admission of the patient and the initiation of GC administration. Many physicians are not familiar with the life-threatening character of adrenal crisis. Efforts are needed to substantially reduce the time to parenteral administration of GCs after arrival of emergency health care professionals. Several improvements were suggested by Hahner et al.;\[89\] emergency physicians should be better trained and an HC injection kit should be carried on every ambulance, similar to the availability of adrenaline for treatment of anaphylaxis. Another strategy could
focus on improved self-management by the patient and their relatives. Patient education is an integral part of patient care in AI. In addition to providing knowledge on GC increases in stress, it would be useful to include assertiveness training of patients and relatives to achieve treatment more rapidly in case of initial refusal of parenteral GC administration by health care professionals. Another potentially helpful measure could be a hotline for emergency calls or the implementation of an alert system in hospital electronic patient records.\textsuperscript{[89]} Treatment of adrenal crisis is well standardized and patients almost invariably respond well to therapy. Improved education of emergency physicians and promotion of self injection of HC by patients or their relatives are key elements to eliminate death from adrenal crisis in patients with known chronic AI.\textsuperscript{[89]} Physicians should provide families with a letter that explains diagnosis and management of AI. All AI patients should wear a medical alert tag listing diagnosis and medication.

**Maintenance therapy**

The suggested physiologic replacement dose of HC in pediatric patients is usually 8-10 mg/m\(^2\) per day divided into two or three doses. In patients with ACTH deficiency, doses closer to 8 mg/m\(^2\) per day administered twice daily may be sufficient. The relative potency must be considered when treating with GCs other than HC (Table 5).\textsuperscript{[88]} Dosage adjustments are clinically based and titrated to a the minimum needed to control the symptoms. Doses may be personalized owing to a wide variability of individual sensitivity to GCs probably caused by polymorphisms in the GC receptor.\textsuperscript{[53,54]}

In primary AI, mineralocorticoid replacement is also required. Fludrocortisone is currently the only available mineralocorticoid and it is given at a dosage of 0.05-0.1 mg/day orally. Treatment with fludrocortisone is effective only if adequate salt is taken (1-2 g/day or 17-34 meq Na). Concomitant hyperandrogenism complicates replacement therapy in patients with 21 hydroxylase deficiency. Doses of HC are higher (9-17 mg/m\(^2\) per day) to suppress ACTH (and therefore adrenal androgen production).\textsuperscript{[90]} In patients with multiple hormone deficiencies, it is important to initiate cortisol replacement at least one week prior to replacement of thyroid hormone, because thyroid hormone accelerates the metabolism of GCs and mineralocorticoids and may precipitate adrenal crisis. Growth hormone has also been shown to affect the metabolism of cortisol through inhibition of 11-\(\beta\)-hydroxysteroid dehydrogenase type 1, which catalyzes the conversion of cortisone to active cortisol. Consequently, circulating cortisol levels are reduced, necessitating adjustment of HC dose may be required once GH replacement is commenced. The effectiveness of treatment should be monitored clinically (e.g., blood pressure, growth velocity, weight and skin pigmentation) and by laboratory testing (e.g., ACTH, renin, androgen precursors, serum electrolytes and fasting serum glucose depending on the etiology of AI).

**Stress glucocorticoid dosing**

Glucocorticoid doses must be increased two to four times the replacement dose during physiologic stress, depending on the stessor. Minor infections with low-grade fever (<38 °C) may not require a change in dose. In children unable to tolerate oral therapy, intramuscular injection of HC should be given and the patient should seek medical attention within six hours of injection. General anesthesia increases GC needs, in addition to the stress of the surgery itself. Typical regimens during surgery include administration of intravenous bolus at the beginning of surgery, followed by varied regimens postoperatively depending on the procedure and the expected degree of stress.\textsuperscript{[88]}

There are many potential adverse effects of GC treatment, including hypertension, hyperglycemia, weight gain, osteoporosis, and gastric ulcers. In children with long-term GC replacement, growth suppression is a concern. Long-acting synthetic GCs (e.g., prednisone and prednisolone) have been shown to have negative effects on growth and are not recommended in growing children. Therefore the alternative GC would be hydrocortisone. When growth velocity decreases, the GC dose may need to be lowered.\textsuperscript{[55]}

Bone mineral density should be assessed annually with bone densitometry in children older than 5 years. Dietary intake of calcium and vitamin D should be assessed and supplemented as needed.

Current GC therapy does not mimic the circadian rhythm of cortisol excretion. GC preparations that mimic the circadian rhythm are currently being tested in clinical trials in adults. However, these formulations have not been tested in children and adolescents.\textsuperscript{[91-93]}

**Table 5. Comparison of the anti-inflammatory, mineralocorticoid, growth suppressing, and androgen suppressing side effects of commonly used steroids**

<table>
<thead>
<tr>
<th>Steroids</th>
<th>Anti-inflammatory effects</th>
<th>Growth suppressing/glucocorticoid effect</th>
<th>Androgen suppressing effect</th>
<th>Salt retention, mineralocorticoid activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>5-15</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>3.5-4</td>
<td></td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td></td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td>30</td>
<td>0-100</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30</td>
<td>0-100</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>15</td>
<td></td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>
Androgen (e.g. dehydroepiandrosterone sulfate) replacement is not needed during childhood.\[^{94}\] In adults, larger scale phase 3 studies are lacking; therefore, initiation of DHEA replacement is decided on an individual basis, focusing on those patients with impaired well-being associated with signs and symptoms of androgen deficiency.\[^{95}\]

**Special management considerations**

**Iatrogenic adrenal insufficiency due to glucocorticoid withdrawal**

There is a lack of consensus on how to withdraw GC therapy and the key point is that it should never be abrupt. When therapy has been chronic, the main objective is to reduce the therapeutic dose to a physiologic level and then proceed with slower withdrawal thereafter in order to permit the HPA axis to recover. In patients receiving GC therapy due to a chronic disease, it is suggested that all available data regarding the clinical and biochemical findings of the disease are retrieved before tapering therapy. Patients whose underlying disease has resolved can have their GC doses tapered more quickly to the physiologic dose. Should signs of GC withdrawal or AI develop whilst tapering, the current dose should be increased or be maintained for longer periods. The reduction of dose should ideally be 20%-25% every 2-4 days until a physiologic dose (8-10 mg/m\(^2\) per day oral HC) is reached. After reaching the physiologic dose, morning serum cortisol and ACTH should be assessed monthly until they normalize. Subsequently, the low-dose ACTH test is performed and the postcorticotropin cortisol level exceeds 500-550 nmol/L (18 - 20 μg/dL).\[^{61}\]

Documentation of an intact HPA axis should be obtained before operating on a patient who has a known history of high-dose long-term GC treatment to surgery. This task may be accomplished by documenting a plasma cortisol level of more than 276 nmol/L (10 μg/dL) taken at 8 hours in the morning. If the gold standard tests of AI cannot be obtained in time, then treating patients with supplemental stress GC coverage in the perioperative period within 1 year of withdrawal of therapy is safest.\[^{77}\]

**Neonatal adrenal insufficiency**

Premature neonates and infants with hemodynamic compromise unresponsive to conventional therapy are given a trial dose of intravenous HC at a bolus dose of 1 mg/kg. If the hemodynamic status begins to improve, HC is repeated at a dosage of 0.5 mg/kg every 12 hours in preterm neonates and every 8 hours in term neonates.\[^{70,71}\] On follow-up, if the basal cortisol is >414 nmol/L (15 μg/dL) or if there is no response to HC, the treatment should be stopped. Otherwise, HC is continued for 72 hours. Caution should be taken while HC is given with ibuprofen or indomethacin due to risk of intestinal perforation.\[^{70}\]

**Critical illness-related corticosteroid insufficiency**

In the critically ill patient, CIRCI is a dynamic and reversible process. Hemodynamic instability, catecholamine dependency and hypoglycemia are strong indicators to initiate GC therapy. If the random cortisol level is <276 nmol/L (10 μg/dL), stress dose of GCs may be started without the need for dynamic testing.\[^{79}\] If the random cortisol is between 276- 938 nmol/L (10-34 μg/dL) and the 250 μg ACTH test reveals a delta cortisol of <248 nmol/L (9 μg/dL), GC treatment is indicated.\[^{79}\] However, no evidence-based guidelines on diagnosis, definition and treatment of CIRCI exist.

**Conclusions**

AI is a well-defined entity with a clinical spectrum that ranges from sub-clinical biochemical abnormalities to full-blown adrenal crisis. In subtle cases, the diagnosis of AI usually requires dynamic tests to be performed. The HPA axis may be affected in different points along the hormonal pathways and to a varying degree, emphasizing the need for individualized diagnostic and treatment approaches. Salivary cortisol seems promising in disorders with aberrations in CBG and albumin levels. However, further studies are required to assess the use of salivary cortisol in the diagnosis of AI. Hemodynamic compromise, vasopressor resistant hypotension, and hypoglycemia are strong indicators to initiate treatment with GCs in AI.

**Acknowledgements**

The authors would like to thank David Chapman for editing this manuscript.

**Funding:** None.

**Ethical approval:** Not applicable.

**Competing interest:** The authors have nothing to disclose.

**Contributors:** Uçar A wrote the main body of the article under the supervision of Baş F and Saka N. Saka N is the guarantor.

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