Endotext

ADRENAL INSUFFICIENCY IN CHILDREN

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ABSTRACT

Adrenal insufficiency (AI) is an uncommon but potentially life-threatening condition related to impaired secretion of cortisol by the adrenal gland. In general, this condition can be divided into primary (adrenal failure) and central (hypothalamic/pituitary) causes. In this chapter, we categorize the causes of adrenal insufficiency and systematically review the etiologies and associations to guide the laboratory evaluation and treatment, specifically as it pertains to the pediatric patient. Early diagnosis and treatment can prevent the development of adrenal crisis – prompt recognition can be lifesaving. Understanding the manifestation of unique types of adrenal insufficiency can guide management with glucocorticoid +/- mineralocorticoids and guide further investigation for associated disorders. We discuss the treatment of adrenal insufficiency, reviewing both the acute (crisis) and chronic management.

INTRODUCTION

Adrenal insufficiency (AI) refers to impaired cortisol secretion by the adrenal gland. If untreated, AI can be life-threatening, especially when it is compounded by a physiological stress, such as an acute illness, severe trauma, or surgical procedure (1,2).

Cortisol secretion is regulated by the hypothalamic-pituitary-adrenal axis (HPA) (Figure 1) (1,2). In brief, Corticotropin-releasing hormone (CRH) secreted by the paraventricular nuclei of the hypothalamus stimulates adrenocorticotropic hormone (ACTH) production and release by the pituitary, leading to cortisol synthesis and secretion by the adrenal gland. Cortisol then negatively feeds back to inhibit both CRH and ACTH release. Clinical manifestations of this feedback mechanism occur frequently as illustrated in clinical practice after chronic treatment with exogenous glucocorticoids, which may suppress CRH and ACTH secretion and consequently result in adrenal atrophy and AI. In addition, a high day (light) and low night (dark) diurnal cycle of ACTH release is entrained, permitting optimal times for assessing the status of spontaneous cortisol secretion (early morning) or its optimal suppression (around midnight).

The fetal adrenal gland markedly differs in structure and function from that of the adult (3,4). During both early and late gestation, the adrenal cortex consists primarily of the fetal zone, which produces predominantly androgens that are critical for the sexual maturation of fetal external genitalia. Early cortisol production is indirect via placental conversion of progesterone synthesized in the fetal adrenal to cortisol, whereas, toward the end of the 2nd trimester, direct cortisol synthesis occurs in the definitive zone of the fetal adrenal (5). Aldosterone synthesis remains low until the end of gestation at which time *CYP11B2* expression begins. After birth, the fetal zone undergoes atrophy via apoptosis, while the zona glomerulosa and zona fasciculata differentiate from the definitive zone to secrete aldosterone and cortisol

respectively, whereas the zona reticularis starts its development postnatally and does not complete development until just before adrenarche (3,4).This process is fully described in the Endotext.org chapter, “Adrenal Cortex: Embryonic Development, Anatomy, Histology and Physiology” (6). The distinctive function of fetal zone and the transition from fetal to adult adrenal function have clinical applications in the very preterm infants who may have transient signs of relative AI after birth (7-9). Furthermore, babies who have a defect in steroidogenesis can present with both adrenal insufficiency and genital atypia (10). The most classic example in this category involves 46,XX babies with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency who present with virilization and adrenal crisis (11). In this chapter, we discuss CAH in the context of AI. Additional information on CAH can be found in the Endotext.org chapter: Congenital Adrenal Hyperplasia (12) https://www.ncbi.nlm.nih.gov/books/NBK278953/. Mineralocorticoid deficiency will be reviewed in the context of primary adrenal insufficiency (PAI), but in-depth coverage of mineralocorticoid deficiency will be included elsewhere as a separate chapter.

PATHOPHYSIOLOGY & CLASSIFICATION

Adrenal insufficiency is classified into primary and central origin (Figure 1) (10,13,14).

Primary AI

Primary AI (PAI) refers to the destruction or dysfunction of the adrenal cortex, often resulting in combined cortisol and aldosterone deficiencies due to injury to both the zona fasciculata and zona glomerulosa (15,16). In cases of destruction, clinical presentation occurs when most of the cortex, >90%, is destroyed. Initial stages may be indolent and may often be followed by an acute stressor leading to clinical presentation and adrenal crisis. In contrast, in cases of dysfunction (i.e. steroidogenesis defects like 21-hydroxylase deficiency causing classical CAH), crisis can occur in the first few weeks of life if the steroidogenic defect is not detected promptly and in the absence of an acute stressor (17). In all cases, decreased glucocorticoid production and decreased negative feedback to the hypothalamus and pituitary result in increased production of ACTH and its pro-hormone pro-opiomelanocortin (POMC) (1). The increase in melanocyte-stimulating hormone (MSH) is responsible for the well-recognized hyperpigmentation present in PAI and often the clinical clue to evolving AI.

Central AI

Central AI involves disorders of the hypothalamic-pituitary region that impair CRH and/or ACTH secretion, and therefore, cortisol production. Aldosterone secretion in the zona glomerulosa of the adrenal cortex is primarily regulated by the renin-angiotensin system rather than ACTH and, thus, remains intact in central AI. Despite the intact mineralocorticoid secretion, hyponatremia may occur due to absence of the glucocorticoid regulated tonic suppression of ADH resulting in volume expansion, a clinical picture similar to the syndrome of inappropriate ADH secretion (SIADH) (18).

SYMPTOMS

Acquired AI can have an insidious onset. Children may present with slowly progressive or nonspecific symptoms, such as anorexia, weight loss, morning nausea or vomiting, and fatigue, which may lead to diagnostic challenges and delayed diagnosis. One cross-sectional, retrospective adult study reported that only 15% of cases were correctly diagnosed at the initial presentation and nearly half had experienced symptoms for more than 1 year before establishing their diagnosis (19). Congenital AI usually presents early in life with signs of adrenal crisis or hypoglycemic seizures. Newborns with central AI may be completely asymptomatic until physical stress elicits an adrenal crisis.

In the pediatric population particularly, specific signs and symptoms should alert the clinician to the possibility of AI. In central AI, central nervous system (CNS) or midline defects may be present. Furthermore, in the neonate, cholestasis may occur due to immature bile acid synthesis and transport (20,21). Virilization and non-palpable gonads associated with the hyperandrogenemia in 46,XX individuals point to classical CAH due to 21-hydroxylase deficiency at birth (22). 46,XY babies with CAH, however, would not present with ambiguity and, thus, may escape medical attention to present with salt-wasting crises between the first and second weeks of life. The inclusion of 17-hydroxyprogesterone measurement in newborn screening programs has enabled detection of these babies prior to the onset of crisis. While the majority of individuals with classical CAH due to 21-hydroxylase deficiency are identified by newborn screening, false negative results and therefore missed diagnosis have been reported (23-26). Moreover, other certain rare enzyme deficiencies are not included in the newborn screen. Thus, a keen clinical index of suspicion remains crucial in cases of CAH who have escaped the newborn screening as experts continue to consider methods to enhance the testing accuracy (27,28). Other associations are discussed in detail under the heading of etiology and are reviewed in Table 1.

In acquired PAI, patients may experience salt craving (i.e., a sign of mineralocorticoid deficiency) and orthostasis and may be noted on examination to have bronze hyperpigmentation, especially in non-sun-exposed areas with prominence in the palmar creases, oral mucosa, skin folds, and areola.

In the case of adrenal crisis, glucocorticoid deficiency may progress to vomiting, muscle weakness, lethargy, hypoglycemia, and ultimately hemodynamic instability. Mineralocorticoid deficiency causes hyponatremia and hyperkalemia and, thus, symptoms may include headache, dizziness, abdominal pain, diarrhea, and ultimately severe dehydration and hypotension. Early detection is critical given the high morbidity and mortality associated with adrenal crisis (29).

ETIOLOGY

Both primary and central AI can arise neonatally due to congenital causes or later in childhood, adolescence and beyond due to acquired causes. In contrast to adults, genetic defects are more likely to be prevalent in infants and children. In recent years, knowledge and understanding of the genetic causes of AI have significantly increased and include every step of the hypothalamic-pituitary-adrenal axis responsible for cortisol and aldosterone synthesis and action (Figure 1 and Table 1).

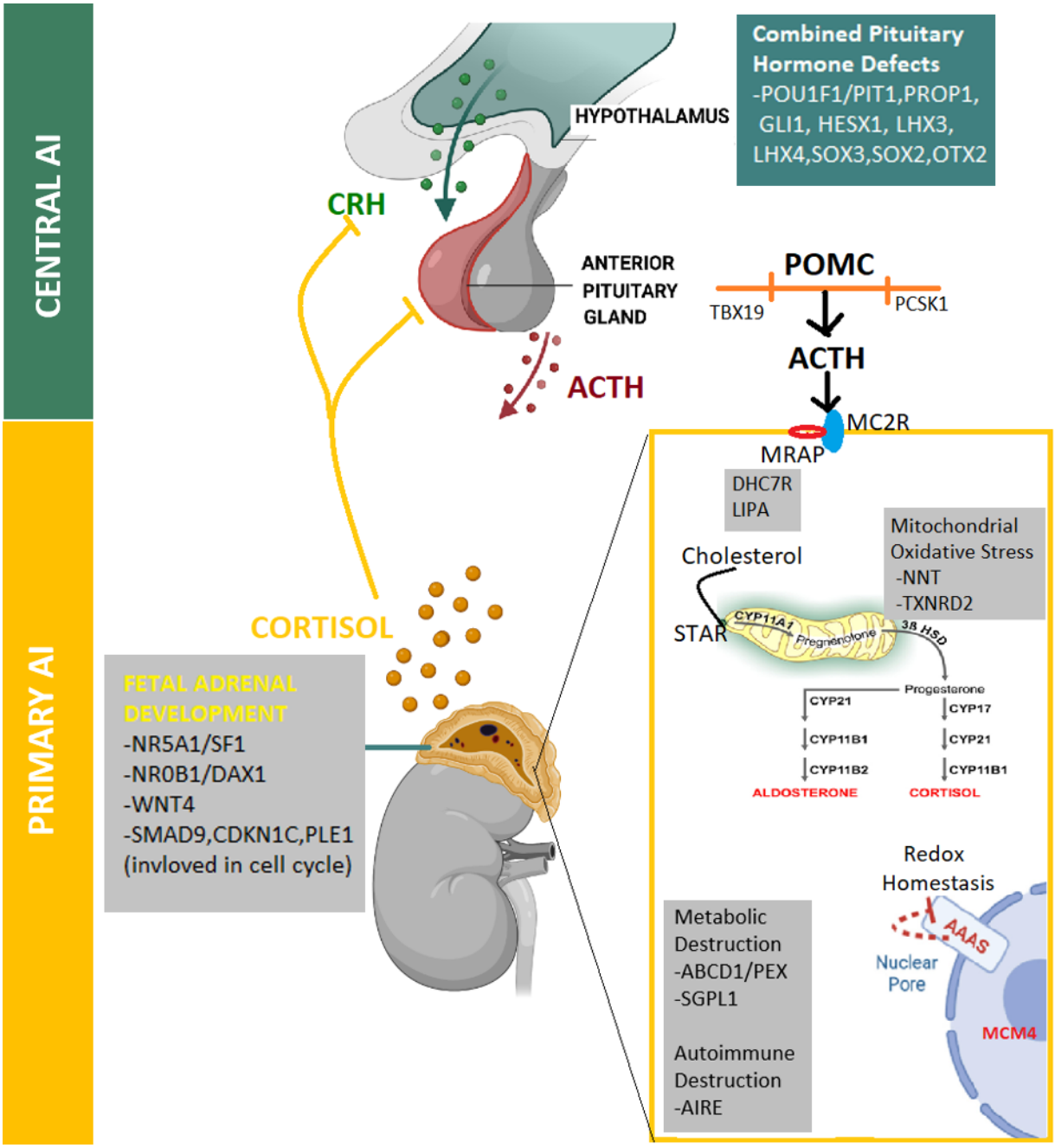

Figure 1. Genetic defects in various steps along the hypothalamic-pituitary-adrenal (HPA) axis can result in either central or primary adrenal insufficiency depending on the location in the pathway. This figure displays the HPA axis and the location operative in the genetic defect, guiding the assessment of central or primary insufficiency. Genetic causes of central AI can include several genes involved in the development of the pituitary gland (e.g., *PROP1, POU1F1 (*formerly *PIT1*), *GLI2, HESX1, LHX3, LHX4, SOX3, SOX2, OTX2*), and result in multiple combined pituitary deficiencies. Central AI can result from an isolated ACTH deficiency caused by defects in the synthesis of pro-opiomelanocortin (*POMC*) or its cleavage. Defects of the melanocortin 2 receptor (MC2R) or its accessory protein MRAP result in ACTH-resistance (a.k.a. as Familial Glucocorticoid Deficiency). There are multiple genetic causes leading to primary AI (PAI). They range from genes that are involved in the development of the adrenal gland

resulting in adrenal hypoplasia, defects in cortisol synthesis itself, or metabolic and autoimmune diseases (e.g. adrenoleukodystrophy, sphingolipidosis or autoimmune polyglandular syndrome), that result in destruction of the adrenal gland over time. Defects in steroidogenesis involve multiple genes along the pathway of cortisol synthesis and are the most frequent cause of PAI. Finally, PAI can be part of certain syndromes, such as Triple A Syndrome (AAAS) or disorders associated with oxidative stress.

Causes of Primary AI

CONGENITAL CAUSES

Disorders of Steroidogenesis

Disorders of steroidogenesis include 1) defects in the cholesterol biochemistry including Smith-Lemli-Opitz (*DHCR7) (30),* 2) early steroidogenesis defects such as congenital lipoid adrenal hyperplasia (*STAR)* and *CYP11A1* mutations (31,32), and 3) defects within the adrenal gland causing CAH, the most common being *CYP21A2* (21-hydroxylase deficiency) and rare forms including *CYP11B1* (11β-hydroxylase deficiency)*, 3HSD2* (3β-hydroxylase deficiency)*, CYP17A1* (17α-hydroxylase deficiency)*, and POR* (Cytochrome P450 oxidoreductase deficiency) (12) (See Fig 2 for depiction of adrenal steroidogenesis, Table 1 for further information on clinical presentations and associations and refer to the Endotext chapter on CAH for further details.)

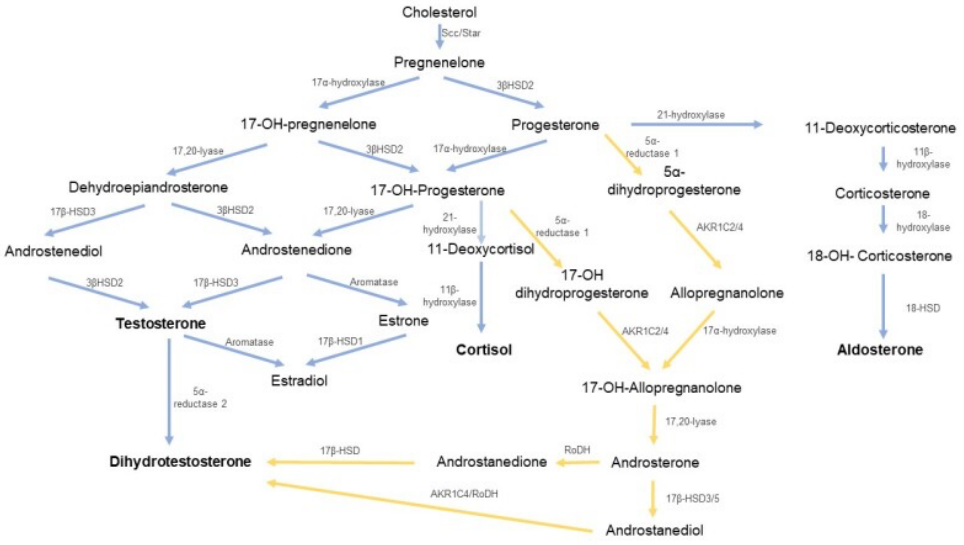

Figure 2. The classical and backdoor pathways of adrenal steroidogenesis: The classical pathway is highlighted in blue, and the backdoor pathway is highlighted in orange. In the classical pathway, five enzymatic steps are necessary for cortisol production. In the first step of adrenal steroidogenesis, cholesterol enters mitochondria via a carrier protein called steroidogenic acute regulatory protein (StAR). ACTH stimulates cholesterol cleavage, the first and rate limiting step of adrenal steroidogenesis. The five enzymes required for cortisol production are cholesterol side chain cleavage enzyme (SCC), 17α-hydroxylase, 3β-hydroxysteroid dehydrogenase (3βHSD2), 21-hydroxylase, and 11β-hydroxylase. The backdoor pathway is an alternative pathway producing dihydrotestosterone. The enzymes include 5α-reductase 1, aldo keto reductases, retinol dehydrogenase RoDH, 17β-hydroxysteroid dehydrogenases, 17α-hydroxylase. *(Figure from CAH Endotext Chapter).*

Adrenal Hypoplasia

Underdevelopment of the adrenal glands may occur as an X-linked genetic disorder (*DAX1/NROB1* – X-linked AHC) and results in both glucocorticoid and mineralocorticoid deficiency (33,34). X-linked AHC is associated with hypogonadism and in some cases, muscular dystrophy. Adrenal hypoplasia can be seen as part of syndromic undergrowth disorders including IMAGe and MIRAGE (35), or in association with gonadal dysgenesis and sex reversal such as *NR5A1 (*formerly *SF1)* (34) and SeRKAL syndrome *(WNT4)* (36) *(see Table 1)*.

ACTH Resistance-Like Conditions

ACTH-resistance, known as Familial Glucocorticoid Deficiency (FGD), is another childhood cause of PAI. It is caused by defects of the melanocortin 2 receptor (MC2R) or its accessory protein at the adrenal gland rendering it unresponsive to ACTH action (Figure 1 and Table 1). Given the specific operative nature of ACTH resistance, concerns for mineralocorticoid insufficiency are rare (37). In FGD type 1, the MC2R receptor is dysfunctional. Patients may present with hyperpigmentation, jaundice, hypoglycemia, and early adrenal crisis or later in life with hyperpigmentation and fatigue (38). In FGD type 2, the MC2R receptor is absent. These cases are due to deficiency of the MRAP (melanocortin 2 receptor accessory protein) which assists in trafficking of the MC2R receptor to the cell surface.

Other disorders associated with ACTH resistance include those associated with oxidative stress (most commonly defects in nicotinamide nucleotide transhydrogenase [*NNT]* but also described in thioredoxin reductase 2 [*TNXRD2]*), Triple A Syndrome (Allgrove syndrome due to disruption of the Aladin protein [AAAS] ACTH resistance/Addison disease, alacrima (absence or deficiency of ocular tears), and achalasia of the esophagus)**(37,38)**, and disruption of mini-chromosome maintenance 4 (*MCM4)*(37-39).

Metabolic Conditions

Metabolic conditions associated with PAI include mitochondrial diseases – large gene deletions such as Kearns-Sayre and Pearson as well as single gene disorders (*MK-TK, MRPS7, QRSL1, NDUFAF5, GFER*), lysosomal storage disorder (Wolman), sphingolipidosis (SGPL1 deficiency), and adrenoleukodystrophy*(40-42)*. Descriptions and associations can be found in Table 1. In adrenoleukodystrophy, neurologic features can prompt identification. However, neurologic manifestations are absent in adrenal only forms of the disease. Adrenoleukodystrophy is included in the newborn screening programs in some states in the US. However, screening is not yet universal in the US and is rare in other countries. Consequently, a high index of suspicion should be maintained for all boys with unknown cause of PAI, and very long chain fatty acids (VLCFA) should be measured. Prompt diagnosis aids in therapeutic decision- making including hematopoietic stem cell transplant as well as more recent approval for gene therapy (43,44).

Zellweger Spectrum disorders consist of a group of peroxisomal related gene disorders that result in neurological dysfunction, hepatic dysfunction, renal cysts and PAI. Screening for PAI is recommended after the first year of life(45).

AQUIRED CAUSES

Autoimmune Conditions

Addison's disease (autoimmune adrenal insufficiency) is the most common cause of AI in adolescents and adults with a median age of presentation at 11 years (15). While less common in young children, it can be seen in association with other endocrine dysfunctions (poly-endocrinopathy). The best described monogenic

cause is related to a defect in the *AIRE* gene and results in Autoimmune Polyglandular Syndrome type 1 (APS1). Presenting features often include mucocutaneous candidiasis and hypocalcemia related to hypoparathyroidism. In contrast, APS2 is typically of polygenic inheritance and is associated with autoimmune thyroiditis and diabetes mellitus with abnormalities in the DQ and DR genes. Adrenal insufficiency related to APS2 has a later age of onset of about 35 years of age, although pediatric cases do occur (15).

Other Causes of Primary AI

Other acquired causes include hemorrhagic, infectious, and infiltrative conditions. Adrenal hemorrhage should only result in adrenal insufficiency if both glands are affected extensively, as 10% of remaining function is sufficient to retain adrenal activity (46). Unilateral hemorrhage should not cause adrenal insufficiency as the single remaining gland is able to compensate. While adrenal hemorrhage occurs fairly often in traumatic birth delivery, few require treatment and of those that do, most resolve within 3-9 months (47). Waterhouse-Friderichsen syndrome is bilateral adrenal hemorrhage of infectious etiology and described with N. meningitides, streptococcus pneumoniae, and other bacterial infections (48). This adrenal insufficiency may also be reversible upon treatment of the primary infection supplemented with cortisol as needed. In contrast, tuberculous adrenal disease results in necrosis of the gland and is often irreversible unless discovered very early in the course of tuberculosis (49).

Several drugs increase cortisol clearance and may precipitate adrenal crisis or require a dose increase in patients with AI on daily glucocorticoid replacement. These include CYP3A4 inducers such as rifampin, mitotane, carbamazepine, and St. John's wort. Initiation of growth hormone and T4 replacement may also increase cortisol metabolism (50). Medications used for treating excessive glucocorticoid secretion (Cushing's disease) that directly block steroidogenesis (ketoconazole, etomidate, metyrapone, osilodrostat) and the glucocorticoid receptor (mifepristone) can induce adrenal insufficiency (51).

Central AI

CONGENITAL CAUSES

Combined Pituitary Hormone Deficiency

Many genetic causes of hypopituitarism (consisting of loss of ACTH with other anterior pituitary hormones such as GH, TSH, LH/FSH) have been elucidated including *PROP1, POU1F1 (*formerly *PIT1*)*, GH1, GLI2, HESX1, LHX3, LHX4, SOX3, SOX2, OTX2 and others (20,21,52).* These can result in hypopituitarism on its own (non-syndromic) or in a constellation of other associated phenotypic features (syndromic), commonly involving midline defects. Despite a genetic etiology, some conditions including *PROP1* and *GH1* may manifest with ACTH insufficiency later in life. As such, close monitoring of the HPA axis in the setting of other pituitary deficiency is crucial (53).

Isolated ACTH Deficiency

Isolated ACTH deficiency can occur due to disruption of *TBX-19* (formerly known as *TPIT*, required for pro-opiomelanocortin protein transcription), due to defects in pro-opiomelanocortin (*POMC*) or pro-hormone convertase-1 (*PC-1*/*PCSK1*) (20). The classic findings of red hair and pale skin and hyperphagic obesity in *POMC* mutations are related to the inability to produce pigmentation and regulate hunger in the absence of α melanocyte stimulating hormones. Another syndromic description involving ACTH deficiency includes DAVID (deficit in anterior pituitary function and variable immunodeficiency) syndrome which occurs in 2/3 of *NFKB2* mutations.

AQUIRED CAUSES

Brain Lesion or Injury, Infiltrative Disease

Traumatic brain injury, brain tumor, infiltrative (histiocytosis, iron overload), and inflammatory (hypophysitis) disorders can result in pituitary dysfunction and impaired ACTH secretion; additional pituitary hormone deficiencies can also occur frequently with these conditions. Diagnosis of AI in these settings should therefore prompt a complete pituitary workup, including evaluation for central hypothyroidism, growth hormone deficiency, and hypogonadotropic hypogonadism (if in a pubertal child). Pituitary surgery may result in central AI post-operatively and during recovery. In contrast, in cases of brain radiation or developmental differences of the pituitary gland, AI may occur over time, and longitudinal assessment is suggested for affected individuals. Traumatic brain injury has been associated with central adrenal insufficiency in up to 14% of individuals with moderate to severe TBI and 6% of athletes with history of concussion with data coming from the adult population (54,55). Data in children have shown central AI in up to 47% of individuals at 3 months and recovery by 12 months after injury (56).

Transient (Hypothalamic Suppression)

Glucocorticoid induced - Oral glucocorticoid administration above physiologic doses (i.e. Hydrocortisone 8-10mg/m^2/day or equivalent) is associated with HPA axis suppression and subsequent adrenal atrophy after 2-4 weeks of daily use (57,58). Although there is significant interindividual variability, risk factors for AI include dose, frequency, and potency of the used glucocorticoid (59). Adrenal suppression can also be seen with inhaled or intranasal glucocorticoids, especially if their use is combined with intermittent use of oral formulations. Screening for AI has been suggested for children taking high doses of inhaled glucocorticoids (>500µg/day of Fluticasone or equivalent) for more than 6 months (60). Particular attention should be paid to the combination of glucocorticoid therapy and CYP3A4 inhibitors, such as grapefruit juice, as the latter can reduce glucocorticoid clearance, and therefore, augment their efficacy.

Adrenal function recovers once glucocorticoids are discontinued. Time to recovery is variable from 1 to many months, and can be affected by length of exposure, dose, frequency, and glucocorticoid potency (61-63). As such, recovery should be monitored, and stress dosing instructions provided until adrenal recovery.

Through a similar mechanism, successful treatment of Cushing's syndrome and Cushing's disease by resection of the pituitary or adrenal lesion results in a temporary adrenal insufficiency, necessitating replacement until recovery is demonstrated.

Other medications - Various medications have been shown to suppress the HPA axis. This is more frequently seen with long term opiate use (Opiate induced adrenal insufficiency - OIAI) due to tonic inhibition of the HPA axis – in which studies have shown 9 to 29% of individuals with adrenal suppression, potentially with high risk associated with younger age (64). There have also been cases of adrenal suppression with short term opiate use (65). Other medications responsible for adrenal suppression include somatostatin analogues, antipsychotics, and antidepressants.

Critical illness- such as sepsis or severe trauma, elicit a "fight-or-flight" or "stress" response that involves multiple physiological processes, including release of catecholamines and activation of the HPA axis. HPA axis activation results in a rapid rise in circulating ACTH and cortisol. The concept of "relative" AI during critical illness was introduced in the early 2000's based on adult data of patients with septic shock who demonstrated an inadequate cortisol response to endocrine testing. The term "relative AI" was later replaced by "critical illness related

corticosteroid insufficiency (CIRCI)" as these patients typically have "inappropriately" low ACTH and cortisol levels in response to stress.

Changes in adrenal function during critical illness are not fully understood (66). However, current research indicates that there is an initial brief HPA axis activation in response to a critical illness followed by a series of adaptive events that include a reduction in cortisol-binding globulin (CBG)/albumin leading to an increase in free cortisol, prolonged cortisol half-life due to suppressed metabolism in liver and kidneys, and tissue-specific changes in glucocorticoid receptor action (66). These peripheral adjustments increase systemic cortisol availability, and with prolonged illness, may result in central HPA suppression. From the clinical standpoint, endocrine testing (i.e. measurement of serum cortisol at baseline or after ACTH stimulation) can be challenging due to reductions in CBG, with one study noting this reduction lasting 7-8 days in adult patients (67). In terms of treatment, randomized controlled trials of stress dose hydrocortisone in critically ill adults showed inconsistent results on long term mortality (68). Hydrocortisone administration was found to have a positive effect on blood pressure, which can be related the pharmacologic effects of high dose glucocorticoids rather than treatment of CIRCI (66).

Pediatric data on CIRCI are limited. Current pediatric guidelines do not recommend hydrocortisone treatment for children with sepsis who are hemodynamically stable after fluid resuscitation but can be considered in those with fluid-refractory, inotrope-resistant shock (69).

Relative AI of the newborn - Very preterm infants may experience refractory hypotension that is unresponsive to fluid resuscitation and inotropic support but responds to treatment with glucocorticoids (7-9). No other apparent cause, like sepsis, is identified in these cases and electrolyte abnormalities indicative of a mineralocorticoid defect can be observed. It has been suggested that these infants have an attenuated cortical response to stress or relative AI. The term transient adrenocortical insufficiency of prematurity (TAP) has also been used as this phenomenon resolves within the first couple weeks of life (8). Immaturity of the HPA axis both at the level of hypothalamus, pituitary, and the adrenal gland itself have been implicated as the underlying pathophysiology. A late-onset GC -responsive circulatory collapse that occurs within the first 2 weeks of life and responds to therapy with glucocorticoids has also been described (70).

Formal diagnosis is challenging given studies failing to show association of low cortisol concentrations with adverse outcomes (71) while others identifying an association between high cortisol values with both morbidity (intracranial hemorrhage and cerebral palsy) and mortality (72,73).

Neither baseline nor stimulated values of cortisol have shown diagnostic benefit.

Cortisol secretion markedly increases during parturition to assist with lung maturation and transition to life after birth. There are data to suggest that very preterm infants who develop bronchopulmonary dysplasia (BPD) often have relative AI after birth. To address this concern, early low-dose hydrocortisone therapy as prophylaxis for AI was found to be beneficial for survival without BPD, although the treatment was associated with increased risk for spontaneous gastrointestinal perforation (74).

TABLE 1. CAUSES OF ADRENAL INSUFFICIENCY IN CHILDREN			
Congenital - Central	Combined pituitary deficiencies	Non syndromic *(PROP1, POU1F1)*	Variable presentations associated with single or multiple pituitary defects including ACTH deficiency. May include hypoglycemia and/or microphallus
		Syndromic	Associated syndromes include optic cell hypoplasia / septo-optic dysplasia, microphthalmia *(HESX1, SOX2, OTX2)* and various CNS malformations (i.e., holoprosencephaly) with midline defects. Syndromes with hypothalamic dysfunction (e.g., ROHHAD syndrome, Prader- Willi syndrome) can rarely be associated with ACTH deficiency.
	Isolated ACTH deficiency	Defects in *TBX19, POMC* or *PCSK1*	Can present in the newborn with hypoglycemic seizures and jaundice. Associated features (*POMC)*: red hair, hyperphagia/obesity. MC4R agonists can be leveraged to treat obesity. Associated features (*PCSK1)*: malabsorptive diarrhea, obesity, and hypogonadism
Acquired - Central	Brain lesion or injury	Examples: Tumor, hemorrhage, irradiation	Usually associated with additional pituitary defects Immune checkpoint inhibitors can be associated with hyper-autoimmunity and cause hypophysitis and hypopituitarism.
	Infiltrative disease	Examples: iron overload (due to transfusions in thalassemias, hemochromatosis), sarcoidosis, Langerhans cell histiocytosis	Usually associated with additional pituitary defects. Symptoms specific to the underlying causative disorder.
	Transient (hypothalamic suppression)	Glucocorticoid therapy	The most frequent cause of adrenal insufficiency. Adrenal function recovers with discontinuation of daily glucocorticoids.
		Medications	Opiates, somatostatin analogues, antipsychotics and antidepressants
		Treatment of Cushing	Permanent: hypophysectomy

			Transient: post operative for unilateral adrenalectomy, or pituitary lesion
		Critical illness -related corticosteroid insufficiency (CIRCI)	Characterized by a series of adaptions of the HPA axis in response to critical illness, which are still not clearly understood. The beneficial effects of glucocorticoids in sepsis are likely related their anti-inflammatory and blood - pressure support effects rather than treatment of adrenal insufficiency.
Congenital - primary	ACTH resistance	Familial Glucocorticoid Deficiency	Type 1 *(MC2R)*: Presents first weeks of life with severe hypoglycemia, prolonged jaundice
			Type 2 *(MRAP)*: Presents first few months of life with AI
		Syndromic	Triple A (Allgrove) syndrome *(AAAS)*: Associated with alacrimand achalasia of the esophagus presenting in childhood or 2nd decade of life
			Disorders associated with oxidative stress *(NNT, TNXRD2)*
	Congenital Adrenal Hypoplasia	X- linked Adrenal Hypoplasia (DAX-1/*NR0B1)*	Can present with salt losing early on or may present later in childhood Additional features: hypogonadotropic hypogonadism. Associated with a larger Xp21 contiguous gene deletion that can result in Duchene Muscular Dystrophy and Glycerol Kinase deficiency Growth hormone insufficiency in a small subset
		Syndromic	IMAGe syndrome *(*gain of function *CDKN1C, POLE1)*: Additional features: IUGR, metaphyseal dysplasia, GU anomalies
			MIRAGE syndrome *(*gain of function *SAMD9)*: Additional features: Myelodysplasia, infections, restriction of growth, GU variations, enteropathy
			NR5A1 mutation and SeRKAL syndrome *(WNT4)*: Associated with gonadal dysgenesis and sex reversal in 46XX individuals
			Rare reports: Pena-Shokeir syndrome type 1 (*DOK7, RAPSN)*, pseudotrisomy 13, Galloway-Mowat (*WDR73)*, Pallister Hall *(GLI3)* and Meckel-Gruber *(MKS1)*
	Disorders of steroidogenesis	Congenital Adrenal Hyperplasia (CAH)	Due to defects in 21-hydroxylase *(CYP21A2)*: The most common cause of PAI in neonates.

			Presents with salt wasting adrenal during 1st month of life crisis and genital virilization in 46XX individuals. Biomarker: elevated 17-hydroxyprogesterone levels. Included in the state newborn screening in US
			Due to defects in 11β-hydroxylase *(CYP11B1)*, 3β-hydroxysteroid dehydrogenase type 2 *(3HSD2)*, 17α-hydroxylase/17,20-lyase *(CYP17A1)*, P450 oxidoreductase *(POR)*: Variable phenotype depending on the defect. Salt wasting and genital atypia can be present. Biomarker: steroid precursor that accumulates above the specific enzymatic defect
		Defects in cholesterol biochemistry	Smith-Lemli-Opitz *(DHCR7).* Additional features: Microcephaly, cleft palate, syndactyly, polydactyly, congenital heart, atypical genitalia with undescended testis. Biomarker: elevated 7-dehydrocholesterol. AI is rare Wolman disease *(LIPA)*. Additional features: lysosomal storage disorder, hepatosplenomegaly, adrenal calcifications, failure to thrive
		Early steroidogenic defect	Congenital lipoid adrenal hyperplasia *(STAR),* P450 Side Chain Cleavage (*CYP11A1)* mutations: Associated with salt wasting and under-virilization of 46XY individuals. Operative in adrenal and gonadal steroidogenesis Salt wasting crisis in severe P450scc deficiency presents at 7-10 days while in *STAR* deficiency, the onset is more insidious, after 3-4 weeks of age Partial enzyme defect may have less severe presentation
	Metabolic disorders	Sphingosine-1-Phosphate Lyase (SGPL1) deficiency	Results from impaired breakdown of sphingosine 1-phosphate. Additional features: adrenal calcifications, nephrotic syndrome. Ichthyosis, neurologic dysfunction.

		Adrenoleukodystrophy	X- linked *(ABCD1).* Usually presents in childhood. Associated with progressive neurologic deterioration. Zellweger Spectrum disorders *(PEX)*. Associated with neonatal adrenoleukodystrophy, hepatomegaly, chondrodysplasia punctuate, hypotonia, seizures. Biomarker: Elevated Very Long Chain Fatty Acids.
		Wolman	*LIPA* mutation – lysosomal storage disorder with foamy lipid droplet accumulation, adrenal calcification and malabsorption
		Mitochondrial Disorders	Variable Presenting features.
Acquired – Primary	Autoimmunity	Addison disease	The most common cause of acquired PAI. Presents in childhood. Biomarker: 21-hydroxylase antibodies Can be part of autoimmune polyglandular syndrome (APS) type I *(AIRE)* or type II (polygenic) APS 1: other associations include: hypoparathyroidism, chronic mucocutaneous candidiasis, ectodermal dystrophy, autoimmune hepatitis, hypogonadism, pernicious anemia. APS2: other associations include autoimmune thyroiditis, diabetes mellitus
	Adrenal damage	Hemorrhage, Infectious, Infiltration (Tuberculosis, HIV, CMV)	Infectious: Tuberculosis, HIV, CMV Infiltration: neuroblastoma
	Transient	Relative adrenal insufficiency of the newborn	Described primarily in preterm sick infants within 2 weeks of life with signs of refractory hypotension in the absence of apparent cause and associated with electrolyte abnormalities (hyponatremia, hyperkalemia). May be related to immature adrenals in the very preterm infants.
		Treatment of Cushing	Permanent: Bilateral adrenalectomy Medication induced: ketoconazole, metyrapone, osilodrostat, etomidate, mifepristone
		Medication induced	CYP3A4 inducers: rifampin, mitotane, carbamazepine and St. John's wort

Mimickers of Adrenal Insufficiency

In the introduction to this chapter, we discussed the risk of delayed diagnosis of AI given the potential overlapping symptoms of glucocorticoid deficiency with other illnesses. In the same vein, other critical illnesses including sepsis and cardiovascular disease may be mistaken for adrenal crisis, especially in the setting of hydrocortisone responsiveness. In this case, hydrocortisone's inotropic properties may lead to symptomatic improvement but may not be diagnostic of underlying AI.

Further, salt wasting adrenal crisis has findings overlapping with other salt-losing crises in infants including those due to kidney inflammation, infection, and obstruction – presenting with vomiting, hyponatremia, and hyperkalemia due to aldosterone resistance (a transient pseudo hypoaldosteronism) (75,76).

EPIDEMIOLOGY

Primary Adrenal Insufficiency (PAI)

PAI is a rare disease. Its incidence in children is not well established. An epidemiologic study from Finland observed a cumulative incidence of 10/100,000 at 15 years and 13/100,000 at 20 years (15). Studies from Europe that include both children and adults describe a similar prevalence (71).

In adults, the most common cause of PAI is autoimmune disease. In contrast, genetic defects are more prevalent in children. CAH due to 21-hydroxylase deficiency occurs in about 1/15,000 births and is the most frequent cause of PAI in children accounting for 50 to 86% of cases (15,77). As such, the age-related incidence of PAI in childhood is higher in the first year of life and decreases afterwards (15). Autoimmune disease is reported as the second most common cause, either as an isolated disease or as a manifestation of a poly endocrinopathy (i.e. APS 1 or 2) (77,78). Whereas most CAH cases are identified in the newborn period, autoimmune disease typically presents after the first couple years of life. X-linked adrenoleukodystrophy (XALD) is another cause of PAI during childhood with a prevalence in newborn males of about 1/20,000, approximately 80% of whom will develop PAI (79).

In recent years, the number of recognized genetic causes of PAI have significantly increased(Figure 1) (13). Genetic testing for PAI has a high diagnosis rate as illustrated by recent studies of children with PAI of unknown etiology, where genetic analysis established the diagnosis in most of the patients (80,81). The most frequent genes involved in these series were *MC2R, NR0B/DAX* and *CYP11A1.*

Central AI

Central AI is also quite rare with most epidemiologic data available in adult populations. The reported occurrence is about 14-28/100,000 individuals, with greater than 50% occurring because of a pituitary tumor (82-84). A Finnish epidemiologic study reporting single center data over a period of 30 years is one of the only studies of incidence in pediatrics. The study looked specifically at combined pituitary hormone deficiencies, without clearly distinguishing AI, and observed similar proportions in pediatric in comparison with previous adult studies, with 61% of hypopituitarism being acquired and the other 39% congenital (85). Craniopharyngiomas comprise the bulk of pediatric pituitary tumors, and similarly account for one quarter of acquired hypopituitarism, with gliomas following at just over 10% (85). Up to 30% of patients with craniopharyngiomas will present with AI due to the lesion itself prior to surgical manipulation while 77-90% will have post-surgical AI (86,87).

Glucocorticoid induced AI is the most common cause of AI in both children and adults. Glucocorticoids are extensively used in clinical practice for treatment of various disorders, such as asthma, autoimmune and

inflammatory diseases, and cancer (88). In US, approximately 1% of the adult population is on oral glucocorticoids and rates increase in the elderly population (89), while similar rates in children are not well established. In adults, AI has been observed around 48% with oral administration and 7.8% with inhalation (57). Rates of AI in children on inhaled glucocorticoids have been reported around 10%, but results may vary depending on the study (90,91). Adrenal crisis and related deaths have been described in children treated with inhaled glucocorticoids(92,93).

DIAGNOSTIC APPROACH TO A PATIENT WITH SUSPECTED AI

Our diagnostic and differential approach to a child with suspected AI is summarized in Figure 2. Clinical signs and symptoms of AI are non-specific and require a high index of suspicion; when present, the suspected diagnosis needs to be confirmed with appropriate laboratory evaluation. Evaluation typically starts with measurement of serum ACTH, cortisol, and electrolytes. In the case of an emergency, such as suspected adrenal crisis, laboratory evaluation can only be interpreted if obtained prior to administration of glucocorticoids as therapy can influence test results.

The goals of the initial laboratory assessment are to confirm the diagnosis of AI, and then, understand if AI is primary or central. Most cases of PAI, but not all, involve combined glucocorticoid and mineralocorticoid deficiencies. In the case of PAI, therefore, mineralocorticoid function must be assessed with measurements of serum electrolytes, aldosterone, and renin (Figure 2). Details on laboratory assessment and additional dynamic testing are included in the LABORATORY EVALUATION section of this chapter.

The next step is to pinpoint the specific etiology so that management can be individualized. Clinical presentation and symptoms can suggest an underlying etiology and guide additional laboratory assessment. For example, salt wasting adrenal crisis in a newborn should prompt measurement of serum 17-hydroxyprogesterone concentrations to rule out CAH. Vitiligo in a child with PAI suggests an autoimmune process, and the underlying etiology can be confirmed with measurement of 21-hydroxylase antibody titers. AI in a boy with neurological manifestations points to adrenoleukodystrophy and calls for measurements of VLCFA. In many instances, however, the specific etiology cannot be identified. In such cases, genetic testing may be very helpful.

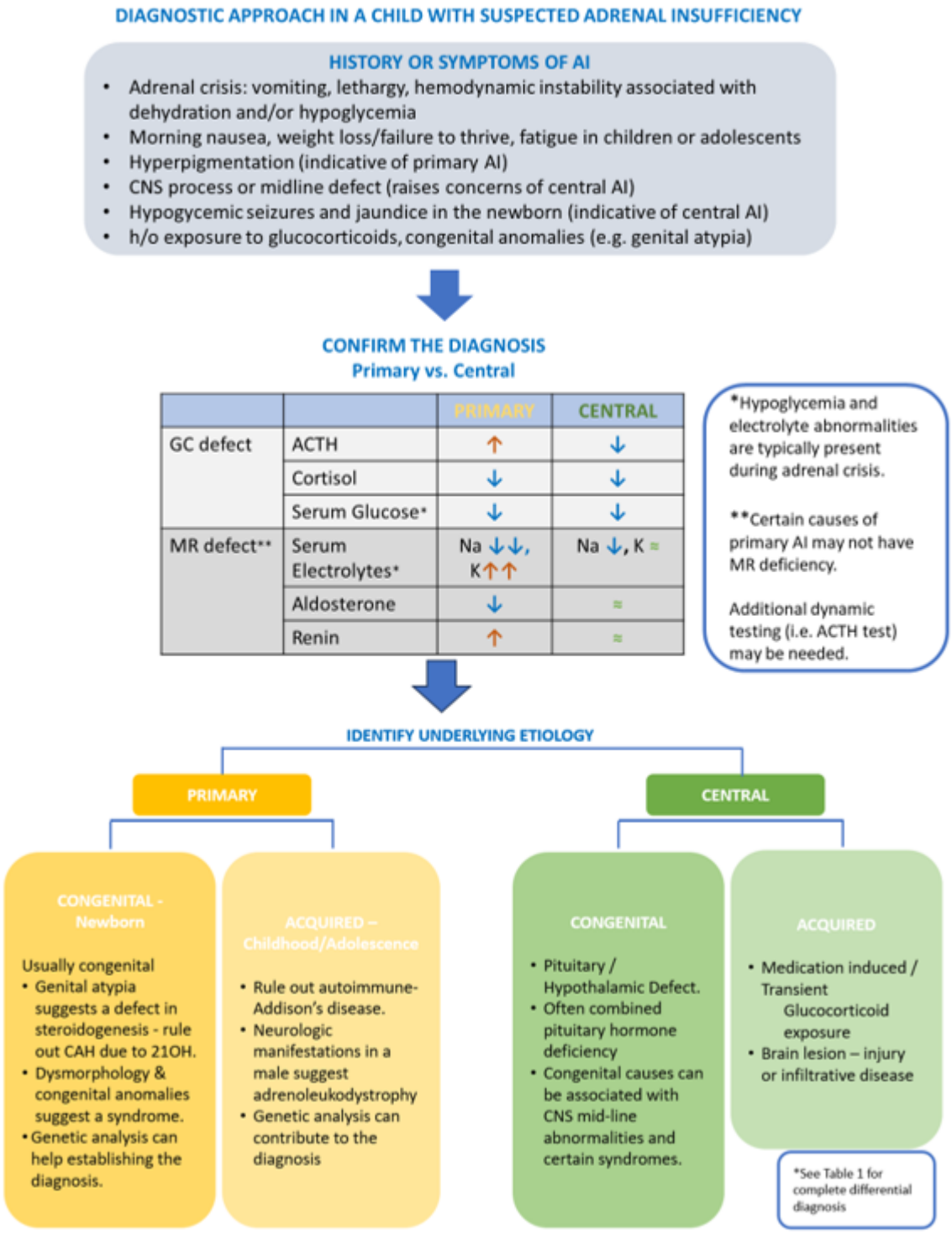

Figure 3. A proposed approach in the diagnosis and differential of AI in children
GC: glucocorticoid. MR: mineralocorticoid. Na: sodium. K: potassium.

LABORATORY EVALUATION

Assessment of Glucocorticoid Function

BASELINE ASSESSMENT OF CORTISOL AND ACTH CONCENTRATIONS

The diagnosis of PAI can be made by measurement of morning ACTH and cortisol concentrations and by demonstrating an inappropriate high ACTH concentration for the cortisol value (Figure 2). Typically, a cortisol value of <5mcg/dL (140nmol/L) associated with an ACTH level > x2 above upper normal range indicates PAI (16). A low morning cortisol value associated with an inappropriately normal ACTH concentration may indicate central AI (94). It is suggested that an 8am cortisol values of <3 mcg/dL (82.8 nmol/ L) in the absence of an elevated ACTH concentration is indicative of central AI (94). Establishing the diagnosis of central AI can be challenging because ACTH concentrations are frequently in the low normal/normal range. The presence of additional pituitary defects increases the risk for AI and needs to be considered when evaluating a child with possible central AI.

Assessment of adrenal function, such as in individuals at risk for glucocorticoid-induced AI, can also start with a measurement of morning cortisol (58,95). Adult studies suggest that an 8am cortisol value of >12mcg/dL can predict normal adrenal function (96,97). It is recognized, however, that various guideline and practice recommendations point to slightly different cut-offs (58,94). Further, the suggested cut-offs need to be interpreted by taking into account the cortisol assay that is used. Of note, the listed cut-offs also do not apply for patients on oral contraceptives and/or estrogen replacement as these medications increase CBG concentrations, and therefore, cortisol values (98).

Morning cortisol values may be unreliable in the newborn as the diurnal pattern of cortisol secretion may take few months to become established (99). Baseline cortisol values have been extensively studied in the sick preterm infant and were not found to be predictive of AI or adverse outcomes (71-73). Furthermore, high cortisol values during first week of life were associated with intracranial hemorrhage and cerebral palsy later in life (73).

DYNAMIC OR STIMULATION TESTS

Stimulations tests are typically performed when the diagnosis of AI needs confirmation. The ACTH (a.k.a. corticotropin or Cosyntropin or Synacthen) stimulation test is the primary test performed in children. Historically, the insulin tolerance test (ITT) has been considered the gold standard test for the diagnosis of AI, but its use has been abandoned as it is associated with severe hypoglycemia (1,16,95). The overnight metyrapone test, an alternative to ITT, is also not routinely performed in children because of potential significant adverse effects (16,95). The CRH (corticotropin releasing hormone) stimulation test has been used in the diagnosis of central AI but there is no evidence that it has greater diagnostic accuracy than ACTH testing in pediatrics and CRH is no longer commercially available (100).

The ACTH test involves the intramuscular or intravenous administration of cosyntropin, a synthetic fragment of ACTH with full biologic activity, along with cortisol measurements at baseline and after cosyntropin administration. Although differences in practice protocols have been described, a common protocol entails cosyntropin doses of 15mcg/kg in infants, 125mcg in children <2years and 250mcg in children older than 2 years (16). Cortisol concentrations are usually measured at 30- and 60-minutes post stimulation, although again, practice variations have been described with the use of the “short” ACTH test that includes cortisol measurement at baseline and only at 30 min after stimulation(101).

The standard dose (250mcg) ACTH test has been validated against the ITT; it has good diagnostic accuracy for PAI but only moderate for central AI (102,103). The low dose ACTH test that involves administration of 1mcg of cosyntropin was developed as an alternative that may offer greater sensitivity in the diagnosis of central AI. Like adult data, however, meta-analysis of pediatric studies indicates that both standard- and low- dose ACTH tests have similar diagnostic accuracy with high specificity but only moderate sensitivity for the diagnosis of central AI (102). These findings suggest that the clinical picture needs to be considered when interpreting ACTH test results. Furthermore, the low dose ACTH test bears technical challenges related to potentially erroneously low administered dose because it requires dilution and cosyntropin is known to adhere to plastic tubing used in intravenous tests (103).

Regardless of the standard- or low- dose ACTH test used, the diagnosis of AI is based on peak cortisol concentrations of 18mcg/dL at either 30 or 60 minutes after cosyntropin (16). The cortisol cut-off of 18mcg/dL was established using cortisol assays of previous methodology that are no longer in use, and therefore, is not applicable in today's clinical practice. Cortisol measured by liquid chromatography with tandem mass spectrometry (LC-MS/MS) is currently considered the gold standard, yet cortisol immunoassays remain widely used in most facilities. Although there no official guidelines or consensus statements at the moment, adult data support revised cortisol cut-offs at 30 min post cosyntropin of around 15mcg/dL using LC-MS/MS and second-generation immunoassays such as Elescys II (Roche Diagnostics) and Access (Beckman Coulter) (101,104,105) . Collectively, the adult data call for revised cortisol cut-offs specific to the assay that is used to avoid overdiagnosis of AI. Limited pediatric data show similar findings as in adults (106).

Literature deriving primarily from critical care medicine uses a cortisol rise of >9mcg/dL during ACTH stimulation to define AI. This criterion is greatly influenced by the baseline cortisol value and has been abandoned (66,95). The ACTH test may miss the diagnosis of AI in newborns with a central defect in ACTH secretion (e.g., septo-optic dysplasia or congenital panhypopituitarism) if it is performed within 1-2 weeks after birth. These babies have normal fetal adrenal function driven by placental CRH stimulation, and therefore, normal response to ACTH stimulation shortly after birth(107). However, they develop adrenal atrophy and insufficiency within the first 2 months of life. Similarly, the ACTH test can be falsely negative if the testing is done during the early stages of AI due to exogenous glucocorticoids or a pituitary/CNS insult and before the atrophy of the adrenals has occurred (95). A high index of suspicion and repeat testing may be needed in such cases. The ACTH test results can be significantly influenced by CBG concentrations. Estrogens are well known to increase CBG concentrations, and estrogen containing oral contraceptives can increase the cortisol cut-off after ACTH stimulation by approximately 10mcg/dL (98,108). Conversely, disease states such as acute illness, cirrhosis, and nephrotic syndrome lead to decreased CBG concentrations and potential overdiagnosis of AI (98). Rare genetic syndromes, such as congenital CBG deficiency or familial glucocorticoid resistance, can also affect baseline as well as stimulated cortisol measurements.

The standard-dose ACTH test is also performed when a disorder of steroid biosynthesis, such as CAH, is suspected. In addition to cortisol, adrenal steroids are measured at baseline and 60-minute post stimulation. Specific nomograms based on 17-hydroxyprogesterone values have been developed for the diagnosis of CAH due to 21-hydroxylase deficiency (12).

Assessment of Mineralocorticoid Function

Electrolytes abnormalities that include hyponatremia in combination with hyperkalemia and acidosis should raise suspicion for a mineralocorticoid defect. The simultaneous measurement of plasma aldosterone

and renin is important for the diagnosis of a mineralocorticoid defect. An inappropriate low aldosterone concentration in the presence elevated renin levels indicates mineralocorticoid deficiency. In such instances, the treating physician needs to carefully assess the glucocorticoid function of the child to determine whether the child has combined deficiencies, such as seen in CAH, or an isolated mineralocorticoid defect, such as seen with aldosterone synthase deficiency. Conversely, markedly elevated aldosterone and renin levels in a child with hyponatremia and hyperkalemia suggest mineralocorticoid resistance, such as pseudo-hypoaldosteronism(109).

Aldosterone and renin concentrations are higher in the newborn and can be affected by prematurity (110-112). Newborns at term have a state of partial aldosterone resistance and hence concurrent high aldosterone values in their blood, that resolve in the first few months of life, whereas babies with severe prematurity have an initial defect in aldosterone secretion followed later by the appearance of physiologic aldosterone resistance (110-112). These physiologic changes need to be considered when assessing mineralocorticoid function in the first few months of life. Lastly, some children with PAI, like those with adrenoleukodystrophy, develop glucocorticoid deficiency initially, while they retain mineralocorticoid activity (79); ongoing monitoring with measurements of serum electrolytes, plasma aldosterone and renin concentrations are required to determine the need for starting mineralocorticoid replacement.

Supporting/Miscellaneous Testing

Once AI is documented, additional testing based on patients' history and symptomatology can pinpoint the specific cause. For example, presence of genital atypia suggests a disorder of steroidogenesis, and elevated concentrations of specific steroid precursors can determine the enzymatic defect (e.g. 17-hydroxyprogesterone in 21-hydroxylase deficiency or 11-deoxycorticosterone in 11β-hydroxylase deficiency) (12). Elevated VLCFA can establish the diagnosis of adrenal leukodystrophy in a boy with AI and neurological manifestations. Positive antibody titers for 21-hydroxylase indicates autoimmune Addison disease. Nonetheless, the underlying cause can be frequently tentative. To this end, genetic testing has become increasingly important. Testing can be tailored according to clinical suspicion and varies from single candidate gene analysis to targeted "panels" or whole exome sequencing (WES). In general, genetic testing for AI has a high diagnostic success rate and can be very helpful in complex cases where diagnosis remains otherwise uncertain (80).

TREATMENT

Hormone Replacement

The goals of daily replacement therapy are to avoid symptoms of adrenal insufficiency while securing optimal growth and weight gain, and appropriate puberal progression.

GLUCOCORTICOID REPLACEMENT

The glucocorticoid of choice for children is hydrocortisone, typically given three time daily (16). The physiologic daily cortisol secretion is approximately 5-8mg/m^2/day (113). In practice, typical replacement doses are 8-10mg/m^2/day, except in CAH which frequently requires supraphysiologic doses to suppress adrenal androgen secretion. The dose distribution during the day usually mimics the diurnal pattern of cortisol secretion with the largest dose given upon awakening, the second dose around noon and the last dose at early evening to avoid overnight hypercortisolemia, which may lead to sleep disturbances, stunted growth, or insulin resistance. A reverse circadian hydrocortisone administration has been used in CAH to suppress the overnight rise in ACTH. This regimen has been criticized as non-physiologic. Individuals with central AI can also be treated with a twice a day regimen (94), with the first

larger dose given upon awakening and the second smaller dose in late afternoon. It is our practice to place children with central AI on a twice a day glucocorticoid replacement regimen, acknowledging that this procedure is based on adult recommendations, while pertinent pediatric data or guidelines are lacking. Specific to children with glucocorticoid-induced AI, hydrocortisone replacement twice a day with the second dose administered in late afternoon can be beneficial and facilitate recovery of the adrenal axis as it avoids nighttime hypercortisolemia and suppression of ACTH secretion.

Challenges with daily hydrocortisone replacement include its short half-life of 60-90min and significant variability in clearance among patients, which result in alternating periods of hypo- and hyper-cortisolemia while on treatment. A modified release hydrocortisone (Plenadren by Takeda Pharmaceuticals International AG Ireland) was designed as a more physiologic and convenient alternative (114). Plenadren provides hydrocortisone released in two phases (i.e., an initial phase of immediate release followed by a phase of extended release) and is given as a once-a day dose upon awakening. It is available in Europe but not in the USA. An additional concern with hydrocortisone administration in young children involves difficulties in dose titration as hydrocortisone is not available in tablets less than 5 mg. To overcome this barrier, hydrocortisone microgranules that provide doses as low as 0.5 mg have been introduced in the market (115). Hydrocortisone microgranules have 1:1 bio equivalency with the standard immediate release hydrocortisone. Finally, it should be kept in mind that certain drugs, like carbamazepine or phenytoin, can induce CYP3A4 in the liver and increase hepatic hydrocortisone clearance requiring higher hydrocortisone replacement doses (11).
Prednisone administered orally once to twice daily can be used as an alternative to hydrocortisone when growth is complete. Use of dexamethasone is not recommended because of difficulties with dose titration and high risk for cushingoid side effects (94).

MINERALOCORTICOID REPLACEMENT

Mineralocorticoid replacement with fludrocortisone at doses 0.05-0.2 mg daily is recommended in patients with PAI and confirmed aldosterone deficiency (16). Higher doses (i.e., 0.1-0.2mg daily) are typically required during the first year of life as newborns have lower mineralocorticoid sensitivity. In addition, infants typically require salt supplementation with sodium chloride, at doses of 1-2 grams daily given in 3-4 divided doses. Treatment with sodium chloride is gradually reduced during the first couple of years of life and replaced with unrestricted salt supplementation with food as the child transitions to regular diet. Extra fluids with electrolytes are recommended when excessive sweating is anticipated, such as during vigorous exercise or hot weather.

MONITORING DURING THERAPY

Monitoring of Glucocorticoid Replacement

There is no good biomarker to assess glucocorticoid replacement. Morning ACTH concentrations are frequently elevated and attempts to normalize ACTH levels may result in overtreatment (16). Measurements of serum cortisol concentrations after hydrocortisone administration is not routinely done. Monitoring of therapy, therefore, relies primarily on clinical assessment. Morning nausea with poor appetite and weight loss can all be signs of inadequate treatment. Children should be questioned about their daily activities and energy during the day (i.e., need for napping after school), and the information should be considered when titrating medication doses. Growth velocity and weight gain are also sensitive clinical indicators. Specifically, overtreatment with glucocorticoids is associated with poor linear growth and an increase in BMI. Appropriate progression through puberty is reassuring.

Monitoring of Mineralocorticoid Replacement

As with glucocorticoids, mineralocorticoid replacement is also assessed clinically starting with questions related to salt craving and measurements of standing blood pressure and heart rate (16). Fatigue and poor growth can also be signs of inadequate mineralocorticoid replacement (95).

Measurements of serum potassium and plasma renin (level or activity) can be used for titration of fludrocortisone dose and sodium chloride supplementation (1,2,16,94). Goals are to maintain serum potassium concentrations in the normal range and plasma renin in the upper range of normal. Orthostatic hypotension, high renin and hyperkalemia indicate undertreatment. On the contrary, low or suppressed plasma renin along with a low serum potassium concentration are signs of mineralocorticoid overtreatment. In such cases, blood pressure needs to be assessed to ensure that the child does not experience hypertension, and fludrocortisone and sodium chloride doses adjusted. In the case of hypertension, one must also remember that hydrocortisone has mineralocorticoid activity and high replacement doses can contribute to blood pressure elevations. Thus, hydrocortisone doses need to be assessed and titrated as needed.

Sick Day Management and Stress Dosing

Endogenous cortisol secretion increases during acute illness, anesthesia, surgery, or trauma. Hence, individuals with AI require an increase in their glucocorticoid doses during times of physiological stress to avoid adrenal crisis.

The stress dose regimens for children are largely empirical or consensus driven and may vary across practices. With lack of good quality evidence, many pediatric recommendations are adopted from adult literature (116). As an overarching principle, stress dose management errs on the side of overtreatment to avoid a potentially life-threatening adrenal crisis.

For management purposes, the stressor is frequently referred to as “moderate” or “severe”. Severe stress refers to major illness (e.g., sepsis), that requires hospitalization, major surgical procedures that require general anesthesia (e.g., abdominal surgery), or severe trauma. Moderate stress refers to an acute illness that can be managed at home or with minor surgery (e.g., a dental procedure) (table 2).

Table 2. Summary of Stress Dose Management of a Child with Adrenal Insufficiency: Indications and Doses				
	Indications	**Hydrocortisone dose**		**Comments**
Adrenal Crisis	Vomiting, lethargy, hemodynamic instability	Age 0-24 months	25mg	♦ *IVF resuscitation with 0.9% sodium chloride/5% glucose* ♦ *Continue with severe stress dose coverage.*
		Age 2yrs - 10 yrs	50mg	
		Age >10 years	100mg IM/SQ	
Severe stress	Surgery, sepsis, major trauma, lethargy, repeated vomiting	100mg/m^2/day divided 6 hours IV/IM Max 50mg every 6 hours		♦ *Wean according to clinical status/improvement.* ♦ *Switch to moderate stress dosing usually when able to tolerate po.*
Moderate stress	Fever >38.3°C (101°F) Significant trauma (i.e., broken bone), Minor surgery requiring anesthesia (e.g., dental procedures), seizures, intense exercise (i.e., marathon)	30-50 mg/m^2/day divided 8 hours orally		♦ *Continue stress dose coverage for up to 24 hours after stress resolves.*
Prednisone can be used as an alternative if hydrocortisone is not available. Dexamethasone is the least preferable option. Additional indications: Minor cold, school exams = no need for stress dosing. Medical procedure with local anesthesia = moderate stress dose orally once prior to procedure.				

MANAGEMENT OF ADRENAL CRISIS

Adrenal crisis is characterized by hypotension and volume depletion. Hypoglycemia is frequent in children. In cases of combined glucocorticoid and mineralocorticoid defects, there is additional urinary sodium loss resulting in electrolyte abnormalities (i.e., hyponatremia, hyperkalemia, acidosis, and elevated serum urea). The cornerstones of therapy are glucocorticoid replacement and fluid resuscitation.

Children with suspected adrenal crisis should immediately receive a bolus dose of hydrocortisone IM or IV (Table 2). For emergencies, a dose based on age can be used, such as 25mg, 50mg and 100mg for children <2 years, 1-10 years, and older than 10 years, respectively. The child should then continue receiving stress dose coverage with parenteral hydrocortisone at doses of 100mg/m^2/day given every 6 hours (maximum dose 50mg every 6 hours) until their condition improves. If hydrocortisone is not available, prednisone (20mg/m^2/day) can be used as an alternative, while dexamethasone (4mg/m^2/day) is the least preferable glucocorticoid option, related to its metabolic consequences as well as lack of mineralocorticoid properties.

Fluid resuscitation can start with a bolus of 0.9% sodium chloride at 10 mL/kg. In the case of hypoglycemia, normal saline with 5% glucose can be used. Fluids should continue based on patient's needs. Hyperkalemia can be severe at the onset of adrenal crisis but improves rapidly with parenteral glucocorticoid and fluid management. Additional therapies to lower serum potassium concentrations can be considered (i.e., IV insulin and glucose, IV calcium gluconate or cation exchange resins) if severe hyperkalemia persists.

MANAGEMENT OF SEVERE STRESS

It entails parenteral administration of hydrocortisone at 100mg/m^2/day given every 6 hours (maximum dose 50mg every 6 hours) (116) (Table 2) Doses can be tapered rapidly and based on clinical improvement to the established daily glucocorticoid regimen. For children recovering from surgery, hydrocortisone can usually be changed to oral sick-day doses once they are stable and can tolerate oral fluids and diet. Children with PAI do not require fludrocortisone during severe stress coverage, as hydrocortisone also has mineralocorticoid activity. Fludrocortisone must be added back to their treatment plan as hydrocortisone is weaned down to approximately 50-60mg/m^2/day.

MANAGEMENT OF MODERATE STRESS OR HOME SICK DAY RULES

Families are advised to increase their child's daily glucocorticoid dose if they experience an intercurrent illness, such as fever or diarrhea (Table 2). Hydrocortisone doses that provide stress dose coverage for such situations (i.e. moderate stress) are in the range of 30-50mg/m^2/day given every 6 or 8 hours (116). A frequent instruction to patients and families is to double or triple the daily hydrocortisone dose. This approach may lead to undertreatment if the daily dose is small. Calculation of a specific moderate stress dose based on the child's body surface area (BSA) is preferable as it provides a more precise dosing.

Stress dose coverage is not recommended for minor upper respiratory viral infections, increased schoolwork, emotional stress, or intense exercise of brief duration. Although there is no specific guideline, some medical providers recommend using stress doses during prolonged intense training, such as a marathon.

Patients and families should undergo in-depth training around stress dose management. Instructions should include indications for moderate stress glucocorticoid administration and appropriate doses and training on using hydrocortisone as an emergency injection IM in case of vomiting, severe trauma, or impending adrenal crisis. They should be provided with a medical letter or card that documents stress dose instructions and contact information of medical providers and caregivers. Children should wear a medical alert bracelet and carry emergency supplies of oral glucocorticoids and emergency injectable hydrocortisone.

Glucocorticoid-Induced Adrenal Insufficiency: Wean and Recovery of Adrenal Function

GLUCOCORTICOID TAPERING

There is no evidence to support a specific approach to GC taper. For individuals on chronic glucocorticoid treatment (i.e., >3-4 weeks) at supraphysiologic doses for an underlying disease (e.g. inflammatory or immune disorder), glucocorticoid taper should be done at a rate dictated by the underlying condition in order to maintain disease remission (58).

Glucocorticoid withdrawal syndrome has been described primarily in adults during tapering of supraphysiologic doses or after successful treatment of Cushing (117). The syndrome can mimic signs of adrenal insufficiency (i.e., fatigue, muscle aches, nausea, abdominal discomfort, weight loss, mood swings, irritability) but is not related to untreated adrenal insufficiency, as the glucocorticoid daily dose

is still supraphysiologic (117). The underlying mechanism is incompletely understood and likely involves cytokine and prostaglandin upregulation as cortisol concentrations decline. Should glucocorticoid withdrawal syndrome be suspected tapering down to physiologic doses can be done at a slower pace (58).

Once physiologic glucocorticoid doses have been achieved, a slower taper below physiologic doses have been suggested (58). The tapering aims to alleviate symptoms of adrenal insufficiency while allowing for HPA axis recovery. For those on long-acting glucocorticoids (e.g., dexamethasone), it is suggested to switch to hydrocortisone to ease with titration at small doses and faster recovery of the adrenal axis. Weaning below physiologic doses is done mostly empirically since there is no evidence about the best practice protocol. It is our practice to wean from physiologic replacement to off glucocorticoids in four-to- five steps by reducing the dose by 20-25% (Table 3). We follow a twice daily hydrocortisone/ prednisone regimen and cut down initially the evening dose to allow for faster HPA axis recovery. Children should remain on a stress dose plan until there is evidence of recovery of adrenal function.

Table 3. Glucocorticoid Induced Adrenal Insufficiency: Proposed Wean From Physiologic Replacement Doses to Off Glucocorticoids

Length of GC exposure	**<4 weeks**	**4-12 weeks**	**>12 weeks**
Hydrocortisone (given twice daily)	No wean	10mg/m^2/day x 4 days	10mg/m^2/day x 7 days
		8mg/m^2/day x 4 days	8mg/m^2/day x 7 days
		6mg/m^2/day x 4 days	6mg/m^2/day x 7 days
		4mg/m^2/day x 4 days	4mg/m^2/day x 7 days
		stop	stop
Prednisone (Given twice daily)	No wean	4mg/m^2/day x 4 days	4mg/m^2/day x 7 days
		3mg/m^2/day x 4 days	3mg/m^2/day x 7 days
		2mg/m^2/day x 4 days	2mg/m^2/day x 7 days
		1mg/m^2/day x 4 days	1mg/m^2/day x 7 days
		Stop	Stop

ASSESSMENT AND RECOVERY OF ADRENAL FUNCTION

Adrenal function recovers once supraphysiologic doses of glucocorticoids are discontinued. The time to recovery, however, is variable and dependent on length and potency of the glucocorticoid that was used (58). Assessment of adrenal function can be done with the measurement of morning cortisol concentrations. Because hydrocortisone interferes in cortisol measurements, testing should be at least 18–24 hours after the last dose. Adult data support a morning cortisol value above 12 mcg/dL as indicative of normal adrenal function, while values less than 5 mcg/dL suggest suppression of the HPA axis. These cortisol cut-offs are dependent on the cortisol assay that is used. An ACTH stimulation test can be considered for intermediate cortisol values (i.e. 5-12mcg/dL). An alternative approach can be to continue stress dose steroid coverage and repeat a measurement of morning cortisol after few weeks and until recovery of the axis is documented.

USEFUL LINKS/GUIDELINES

- *Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 https://pubmed.ncbi.nlm.nih.gov/26760044/*
- *European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and Therapy of Glucocorticoid-induced Adrenal Insufficiency. J Clin Endocrinol Metab. 2024 PMC11180513.https://pubmed.ncbi.nlm.nih.gov/38724043/*
- *Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 https://pubmed.ncbi.nlm.nih.gov/27736313/*
- *Emergency and perioperative management of adrenal insufficiency in children and young people: British Society for Paediatric Endocrinology and Diabetes consensus guidance. Arch Dis Child. 2023 https://pubmed.ncbi.nlm.nih.gov/37045585/*

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