Adrenal Insufficiency

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Educational Gaps

Pediatricians must have increased awareness of clinical and biochemical manifestations of congenital adrenal hyperplasia in newborns to institute appropriate diagnostic workup and early initiation of corticosteroid supplementation. Pediatricians must also have increased awareness of clinical and biochemical manifestations of adrenal insufficiency (regardless of its cause) and institute prompt treatment with corticosteroid supplementation.

Objectives   After completing this article, readers should be able to:

1. Recognize the clinical and biochemical manifestations of congenital adrenal hyperplasia and its different subtypes.

2. Appraise the importance of early administration of corticosteroid supplementation in patients with congenital adrenal hyperplasia.

3. Recognize early the clinical and biochemical manifestations of adrenal insufficiency.

4. Distinguish the different levels of treatment of patients with adrenal insufficiency: long term, stress supplementation, and treatment of adrenal crisis.

Abstract

Adrenal insufficiency is a life-threatening condition that occurs secondary to impaired secretion of adrenal glucocorticoid and mineralocorticoid hormones. This condition can be caused by primary destruction or dysfunction of the adrenal glands or impairment of the hypothalamic-pituitary-adrenal axis. In children, the most common causes of primary adrenal insufficiency are impaired adrenal steroidogenesis (congenital adrenal hyperplasia) and adrenal destruction or dysfunction (autoimmune polyendocrine syndrome and adrenoleukodystrophy), whereas exogenous corticosteroid therapy withdrawal or poor adherence to scheduled corticosteroid dosing with long-standing treatment constitute the most common cause of acquired adrenal insufficiency. Although there are classic clinical signs (eg, fatigue, orthostatic hypotension, hyperpigmentation, hyponatremia, hyperkalemia, and

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
ALD	adrenoleukodystrophy
APS	autoimmune polyendocrine syndrome
CAH	congenital adrenal hyperplasia
HPA	hypothalamic-pituitary-adrenal
PAI	primary adrenal insufficiency

hypoglycemia) of adrenal insufficiency, its early clinical presentation is most commonly vague and undefined, requiring a high index of suspicion. The relevance of early identification of adrenal insufficiency is to avoid the potential lethal outcome secondary to severe cardiovascular and hemodynamic insufficiency. The clinician must be aware of the need for increased corticosteroid dose supplementation during stress periods.

INTRODUCTION

Adrenal insufficiency is a life-threatening condition caused by an impaired secretion of the adrenal glucocorticoid and mineralocorticoid hormones. (1) Adrenal insufficiency was first described in a seminal article by Thomas Addison (2) in the second half of the 19th century, characterizing the syndrome by weakness, fatigue, anorexia, salt craving, and orthostatic hypotension. The most common cause at that time was tuberculosis.

An impaired adrenal steroidogenesis, adrenal destruction, and adrenal dysgenesis are the most common reported causes of primary adrenal insufficiency (PAI) in children. (3) On the other hand, exogenous corticosteroid therapy withdrawal or poor adherence to scheduled corticosteroid dosing with long-standing treatment constitute the most common cause of secondary adrenal insufficiency in children. (4)

The clinician must have a high index of suspicion because the early presentation of adrenal insufficiency may be vague and undefined. The relevance of early identification of adrenal insufficiency is to prevent the potential lethal outcome secondary to severe cardiovascular and hemodynamic insufficiency.

First, we discuss the most common causes and updates of PAI in children, which include congenital adrenal hyperplasia (CAH), autoimmune adrenal destruction, and adrenoleukodystrophy (ALD). (5) Second, we discuss secondary and acquired causes, such as drugs that inhibit steroidogenesis, and infectious and hemorrhagic causes. (5)

IMPAIRED STEROIDOGENESIS

Impaired steroidogenesis is a group of enzymatic defects responsible for cholesterol biosynthesis defects or corticosteroid biosynthesis defects. The most common cause of adrenal insufficiency in infancy is CAH. (6) CAH is a group of autosomal recessive disorders caused by a disruption in the enzymatic pathway of adrenal steroidogenesis, most often a deficiency in the 21-hydroxylase enzyme. (7)(8) This enzymatic defect results in impaired secretion of glucocorticoids. Inefficient cortisol synthesis signals the hypothalamus and pituitary to increase corticotropin-releasing hormone and adrenocorticotropic hormone (ACTH) release, respectively, and the adrenal glands become hyperplastic. (9)

CAH occurs in 1:10,000 to 18,000 live births with variation in some ethnic groups. (10) The most common type, which accounts for 90% to 95% of cases, is due to 21-hydroxylase deficiency, the enzyme that allows the conversion of 17-hydroxyprogesterone to 11-deoxycortisol. Two major phenotypes are recognized with this enzyme deficiency: a classic form and a nonclassic form (Figure 1). (9)

The classic form has a block in cortisol synthesis that leads to ACTH stimulation of the adrenal cortex that in turn leads to an accumulation of cortisol precursors that are redirected toward sex hormone biosynthesis and hyperandrogenism. The net effect is prenatal virilization of girls and rapid somatic growth with early epiphyseal fusion in both sexes.

Approximately 75% of patients with the classic form have aldosterone deficiency with salt wasting and potentially fatal hyponatremic dehydration and shock. This salt-losing form is most often associated with large gene deletions or intron mutations that result in no enzyme activity. (11)

The biochemical and clinical abnormalities of the classic form present both prenatally and postnatally. The condition is usually detected in infant girls in the neonatal period because of genital ambiguity compared with infant boys, who have normal genitalia and, in the case of the salt-wasting form, can present with the nonspecific symptoms of vomiting, dehydration, and poor feeding at ages 1 to 3 weeks. Hence, the diagnosis in boys can be delayed or missed.

For approximately 25% of the classic form, patients present with simple virilization without salt wasting. The simple virilizing form most commonly results from point mutations that lead to amino acid substitution, causing low but detectable enzyme activity that supports sufficient glucocorticoid and aldosterone secretion. (11) If the condition is unrecognized and untreated, both girls and boys undergo rapid postnatal growth and sexual precocity due to hyperandrogenism at approximately ages 2 to 4 years. (9)
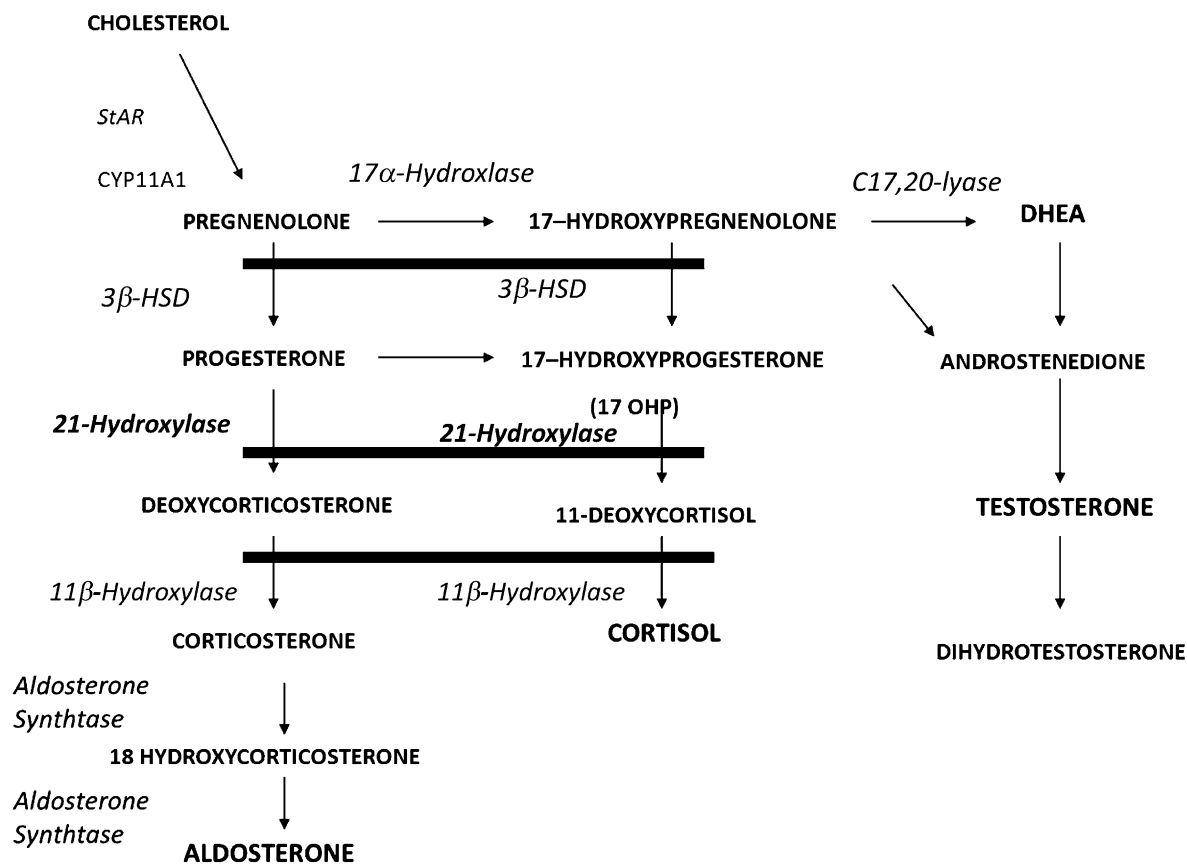
Figure 1. Steroidogenesis pathway.
3β-HSD=3β-hydroxysteroid dehydrogenase; DHEA=dehydroepiandrosterone sulfate; StAR=steroidogenic acute regulatory protein. Adapted from White and Speiser. (9)

The nonclassic form or late-onset form is more prevalent and occurs in approximately 0.1% to 0.2% in the general white population and up to 1% to 2% among Ashkenazi Jews. Girls with the nonclassic form may be compound heterozygotes with a classic mutation and variant allele or heterozygotes with 2 variant alleles, allowing 20% to 60% of normal enzymatic activity. (12)(13)

Compound heterozygote girls usually have a less severe phenotype and a variable clinical presentation; they may present at any age but usually not earlier than 6 months. Heterozygote girls may have mild biochemical abnormalities but no clinically important endocrine disorder. (11)

Because of the fatality and potential misdiagnosis of the salt-wasting classic form of CAH, newborn screening programs have been established. Since 2009, all 50 states in the United States and 12 other countries screen for CAH. Measurement of 17-hydroxyprogesterone concentration from a dried filter paper blood spot is typically performed by many screening programs.

Newborn screening is sufficiently specific and sensitive to detect almost all infants with classic CAH and some infants with nonclassic CAH. (14)(15)(16) Although false-negative results are uncommon, false-positive results are usually seen in premature infants; therefore, serial measurements of 17-hydroxyprogesterone are advised for premature infants.

A positive screening result needs to be confirmed by a validated serum or plasma 17-hydroxyprogesterone sample. CYP21 molecular genetic analyses confirm the enzymatic defect, which helps to establish the diagnosis in uncertain cases and to aid in genetic counseling. However, CYP21 molecular genetic analysis is not essential for the diagnosis. Figure 2 shows a flowchart for decisions that pertain to newborn screening for 21-hydroxylase deficiency. (14)(15)

Newborn screening efforts and enhanced clinician awareness of abnormal phenotypes have markedly reduced the morbidity and mortality related to CAH. Female newborns with ambiguous external genitalia require urgent expert medical attention. Table 1 gives the normal hormone values for full-term and preterm infants from 2 hours postnatally to 7 days after birth. (17) Once CAH is excluded, autoimmune destruction of the adrenal gland accounts for approximately 50% of all PAI cases. (6)

Figure 2. Flowchart for decisions pertaining to newborn screening for 21-hydroxylase deficiency.
17OHP=17-hydroxyprogesterone; ACTH=adrenocorticotropic hormone; CAH = congenital adrenal hyperplasia; PRA/Aldo = ratio of plasma renin activity to aldosterone. Adapted from Joint LWPES/ESPE CAH Working Group. (14)
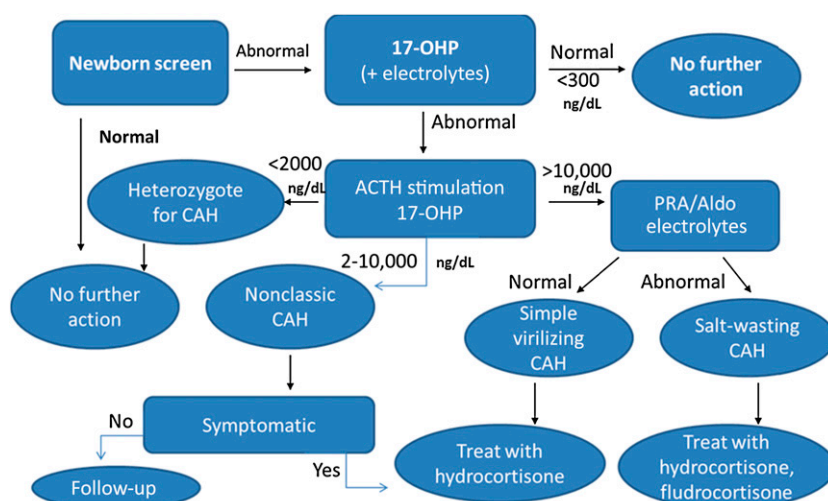
ADRENAL DESTRUCTION AND ADRENAL DYSFUNCTION

PAI (known as Addison disease) is the consequence of the impaired function or the destruction of the adrenal cortex caused by genetic mutation, infection, autoimmune process, tumor invasion, or neonatal or postnatal hemorrhage of the adrenal gland. It is a rare disorder with prevalence in developed countries of 90 to 140 per million. (1)

In older children, it usually presents with nonspecific and insidious symptoms, such as fatigue, nausea, abdominal pain, and vomiting. In infants, it can present as poor feeding, decreased alertness, and vomiting with signs of dehydration. Classic biochemical signs include hyponatremia, hyperkalemia, hypoglycemia, and ketonemia.

Hypotension and hyponatremia are usually present at diagnosis; hyperpigmentation and hyperkalemia occur inconsistently in contrast with salt-wasting CAH in which hyperkalemia is almost invariably present. (6) Recent studies indicate that PAI is much more common and undoubtedly missed.

ACTH, renin, and aldosterone levels with high-dose cosyntropin stimulation testing are helpful in confirming the diagnosis of PAI. In PAI, ACTH levels will be elevated, aldosterone levels will be low, and renin levels will be elevated. Early morning (4-6 AM) plasma cortisol levels lower than 3 μg/dL (83 nmol/L) are highly suggestive of PAI, whereas values higher than 15 μg/dL (414 nmol/L) rule against the diagnosis of PAI. The high-dose cosyntropin stimulation test, which includes administering 250 μg of cosyntropin intravenously and monitoring the plasma cortisol value immediately before and 30 and 60 minutes after the injection, can be performed at any time during the day.

TABLE 1. **Mean Normal Hormone Values for Full-Term (FT) and Preterm (PT) Infants From 2 Hours Postnatally to 7 After Birth[a]**

	2 HOURS		24 HOURS		4 DAYS		7 DAYS	
HORMONE	PT INFANTS	FT INFANTS	PT INFANTS	FT INFANTS	PT INFANTS	FT INFANTS	PT INFANTS	FT INFANTS
Progesterone, ng/mL	39	57.3	6.79	12.50	0.56	0.88	0.53	0.50
17-Hydroxyprogesterone, ng/mL	7.13	8.86	2.86	0.94	2.14	0.79	2.37	1.24
Cortisol, μg/dL	8.2	10.4	3.7	2.7	4.5	5.7	3.2	3.5
Deoxycorticosterone, ng/dL	114	360	38	116	9	13	6	11

SI conversion factors: To convert progesterone to nanomoles per liter, multiply by 3.18; cortisol to nanomoles per liter, multiply by 27.588; and deoxycorticosterone to nanomoles per liter, multiply by 0.0303.
[a]Adapted from Feldman Witchel and Lee. (17)

A normal response is reaching a plasma cortisol concentration of at least 18 μg/dL (497 nmol/L) or higher at 30 minutes.

To determine a possible autoimmune cause, serum antibodies against 21-hydroxylase enzyme should be measured in all patients past infancy. Autoimmune destruction of the adrenal cortex is the cause in 45% to 55% of PAI cases in children. (3) Clinical presentation can occur alone or as a component of autoimmune destruction of other endocrine glands.

Approximately 50% of patients, especially female patients, will present with autoimmune polyendocrine syndrome (APS), which is also known as autoimmune polyglandular syndrome. Its phenotype can be of 2 types with specific combinations of involvement of other endocrine organs in addition to autoimmune adrenal insufficiency.

Autoimmune Polyendocrine Syndrome

APS type 1 syndrome (OMIM 240300) occurs secondary to mutations in the *AIRE* gene. It is known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy and is characterized by hypoparathyroidism, chronic mucocutaneous candidiasis, primary hypogonadism, malabsorption, and adrenal insufficiency. (18)

APS type 2 syndrome (OMIM 269200) is more common than APS type 1. It is characterized mainly by PAI; some patients may also develop autoimmune thyroiditis (Schmidt syndrome) or type 1 diabetes mellitus (Carpenter syndrome). Additional manifestations are primary gonadal failure, vitiligo, and autoimmune atrophic gastritis. It usually affects young adults, yet can present in childhood. (19)

Autoimmune adrenal insufficiency is associated with certain genetic predispositions. HLA genotype DR3/4-DQB1_0302 is well known to be associated with APS type 2 adrenal insufficiency and type 1 diabetes. DRB1_0404 allele has been reported in higher frequency among patients with adrenal insufficiency. (20)

Adrenoleukodystrophy

ALD (OMIM 300100) is a peroxisomal disorder of β-oxidation associated with the destruction of the adrenocortical cells, which accounts for 10% of all cases of PAI in children and young men. (21) In the United States, 1 in 21,000 and 1 in 16,800 are hemizygotes and hemizygotes plus heterozygotes, respectively. (22) The defect results from a mutation of the *ABCD1* gene, preventing normal transport of very long-chain fatty acids into peroxisomes, thereby preventing β-oxidation and breakdown of long-chain fatty acids. This results in accumulation of very long-chain fatty acids in all tissues. (23)

X-linked ALD presents as 2 main phenotypes: adreno-myeloneuropathy and the cerebral demyelinating form. Both forms manifest as PAI and progressive neurologic deterioration, dementia, visual impairment, stiffness and weakness of the legs, impaired vibration sense in the lower limbs, and sphincter disturbances.

The cerebral demyelinating form is the most severe and devastating phenotype; 30% to 40% of boys develop symptoms between ages 5 and 12 years. Once a patient develops cerebral demyelinization (usually seen on brain magnetic resonance imaging), the disease becomes inflammatory and progresses rapidly. (23) Approximately 10% of boys may not enter in the active inflammatory stage of the disease, often referred to as chronic or arrested cerebral X-linked ALD. The patient can have a 10- to 15-year period of clinical stability after which there is a high likelihood of full progression to the inflammatory stage of the disease with sudden onset of rapid neurologic deterioration. (24)

The endocrine characteristics of patients with ALD are not different from those with other causes of Addison disease. (25) For ALD, other than replacing adrenal corticosteroids in the case of adrenal insufficiency, dietary therapy with Lorenzo oil appears to have a preventive effect in asymptomatic boys whose brain magnetic resonance imaging findings are normal. Hematopoietic stem cell transplants in patients early in the clinical stages of the cerebral inflammatory phenotype may help. (26)

Newborn screening for ALD is under development. Challenges include establishing protocols for patient follow-up and for counseling parents when newborn screen results are positive for ALD. (23)

Other Causes of Adrenal Dysfunction or Destruction

Rare causes that the pediatrician must be aware of include diseases of cholesterol metabolism, such as Wolman disease and Smith-Lemli-Opitz syndrome; mitochondrial disorders, such as Kearns-Sayre syndrome; and storage diseases, such as Niemann-Pick disease. (27)

Wolman disease is associated with cholesterol ester storage in end organs (liver, spleen, and adrenal glands) and has been reported as the cause of PAI in 3% of cases in a large series. (3)

Smith-Lemli-Opitz syndrome is an autosomal recessive defect in cholesterol biosynthesis, resulting in a clinical spectrum of microcephaly, developmental delay, typical facial appearance, proximal thumbs and syndactyly of the second and third toes, cardiac abnormalities, and underdeveloped genitalia in males. Adrenal insufficiency develops during episodes of stress, especially when dietary cholesterol sources are insufficient. (28)

Primary adrenal insufficiency secondary to mitochondrial disorders is rare in childhood, but when subclinical

adrenocortical insufficiency is present as a component of multiorganic involvement, such as in Kearns-Sayre syndrome, it is associated with a poor prognosis. (27)

The lysosomal lipid storage disease Niemann-Pick disease type B, which occurs secondary to mutations in the *SMPD1* gene, may present with adrenal insufficiency, hepatosplenomegaly, and pulmonary disease. (27)

Secondary Adrenal Insufficiency. Secondary adrenal insufficiency is caused by impaired circulating ACTH with a consequent decrease in adrenal cortex stimulation. The intrinsic causes are due to hypothalamic defects, hypopituitarism, and disorders of pro-opiomelanocortin metabolism. The acquired adrenal insufficiency secondary to HPA axis suppression after exogenous corticosteroid treatment is discussed in the next section. Isolated ACTH insufficiency and disorders of pro-opiomelanocortin are extremely rare. (27)

The hypothalamic causes of ACTH insufficiency include tumors (eg, craniopharyngioma, germinoma, and astrocytoma) and radiotherapy. (29)(30)(31) Pituitary causes of ACTH insufficiency include multiple pituitary hormone deficiency or isolated ACTH insufficiency. (32) Panhypopituitarism can result from pituitary injury (surgery or radiotherapy), from infiltrative process (Langerhans cell histiocytosis or sarcoidosis), or secondary to hypothalamic dysfunction. (27)

Acquired Adrenal Insufficiency. The ubiquitous and long-standing use of long-term corticosteroids for a variety of reasons (eg, asthma, rheumatoid arthritis, vasculitis, and malignant tumor) predisposes patients to the development of chronic adrenal depression secondary to the suppression of ACTH secretion. Clinicians may find this type of adrenal insufficiency more frequently than PAI.

Acquired adrenal insufficiency can occur with all different ways of corticosteroid administration (injectable [intravenous, intramuscular, or subcutaneous], intranasal, inhaled, or topical mucocutaneous). Generally, the cause of acute adrenal insufficiency in these patients is the lack of physiologic increase in endogenous corticosteroid levels during periods of stress (eg, surgery, burns, and critical illness). (33)

Topical Corticosteroid Use

The development of adrenal suppression with topical cutaneous corticosteroid use is associated with high-potency corticosteroids, high doses, long-term use, and application over large skin areas and on severely damaged skin, which predisposes patients to a higher degree of absorption. (34) The clinical manifestations of adrenal insufficiency secondary to topical corticosteroids are similar to those of patients

treated with systemic corticosteroids, including persistent hypoglycemia. (35)

Inhaled Corticosteroids

The use of inhaled (not intranasal) corticosteroids has become more prominent given its recommendation as a chronic asthma controller medication as indicated by the 2007 guidelines from the National Heart, Lung, and Blood Institute. (36) The long-term use of large doses of inhaled corticosteroids for more than 3 to 6 months is associated with acquired adrenal insufficiency during periods of stress. The doses associated with HPA axis suppression are 500 μg/d or more of fluticasone, 1,000 μg/d or more of budesonide and beclomethasone, or more than 1,000 μg/d of ciclesonide. (37)

Presumably, the benefit of long-term corticosteroid use outweighs its potential risk of linear growth suppression and may not necessarily affect the final adult height. However, linear growth may be arrested in children using long-term inhaled corticosteroids. (38) Symptomatic adrenal insufficiency secondary to long-term use of inhaled corticosteroids has been also described. (39)

It is presumed that the chronic proinflammatory state of asthma decreases the level of response of the hypothalamic-pituitary-adrenal (HPA) axis and systemically absorbed corticosteroids are sufficient to compensate for the decreased endogenous corticosteroid production in a nonstress state. (40) Of all the inhaled corticosteroids, fluticasone propionate has the highest suppressive effect on the HPA axis. This finding is most likely secondary to its pharmacologic properties (large volume of distribution, strong affinity for glucocorticoid receptor >18 times of dexamethasone, and prolonged half-life of the fluticasone-receptor binding complex of >10 hours). (41) The use of the lowest possible dose is perhaps the best strategy to prevent the development of adrenal suppression. (42)

Other Medications and Rare Causes

Several medications are associated with the development of adrenal insufficiency: the antifungal ketoconazole; the sedative-hypnotic etomidate, which can cause critical care patients to develop adrenal insufficiency after a single dose; and the vascular endothelial growth factor inhibitors (tyrosine kinase–targeting drugs), such as sunitinib, which has been associated with the development of adrenal hemorrhage. (39) Other drugs associated with the development of adrenal insufficiency include the antiparasitic suramin and the anticorticosteroid aminoglutethimide. (27) Rare causes of acquired adrenal insufficiency in later stages of life include infiltrative disease (eg, metastases, sarcoidosis, and amyloidosis). (43)

Use of Corticosteroids in Patients With Chronic Inflammation and Malignant Tumors (Acute Lymphocytic Leukemia)

The development of adrenal insufficiency in patients with inflammatory disorders is related to duration and cumulative dose of corticosteroids. (44)(45) In adult patients, courses longer than 14 days of high-dose glucocorticoid administration can result in suppression of the HPA axis for 1 year after discontinuation of treatment. (46)

In the past few decades, an impressive increase in survival has been seen in patients affected by acute lymphocytic leukemia; an important component of the chemotherapy regimen is the use of corticosteroids (prednisone or dexamethasone), which have similar rates of adrenal suppression. (47) A 4-week course of glucocorticoids in this population may cause HPA axis suppression for up to 8 weeks after discontinuation. (48)

Infectious Causes

Other relevant causes of adrenal insufficiency are infectious processes. Tuberculosis has long been recognized as a classic cause of acquired Addison disease. Although currently its pathogenic role in the etiology of adrenal insufficiency has decreased to less than 20% of cases in developed countries, thanks to the improvement in the treatment of tuberculosis, it is still a leading cause of adrenal insufficiency in developing countries. (20)(33)(49)

Invasive meningococcemia can cause acute adrenal insufficiency secondary to bilateral adrenal hemorrhage, known as Waterhouse-Friderichsen syndrome. (49) This condition can occur in patients with immunodeficiencies (eg, complement deficiency [mostly terminal components C5–C9], agammaglobulinemia, and asplenia). (50)

Acute adrenal insufficiency has been also associated with systemic bacterial infections by *Pseudomonas* species, streptococci, and *Staphylococcus aureus*. (51) Other chronic infections, including fungal (histoplasmosis and coccidioidomycosis) and viral (cytomegalovirus and human immunodeficiency virus) diseases, can cause adrenal infiltration and subsequent failure. (27)(43)

CLINICAL MANIFESTATIONS

Classic clinical signs of adrenal insufficiency include decreased vascular tone (manifested by orthostatic hypotension or shock) and hyperpigmentation. Classic biochemical signs include hyponatremia, hyperkalemia, hypoglycemia, and ketonemia or ketonuria. In a series of 42 patients, fatigue, poor appetite, hypotension, and hyponatremia were the most prevalent findings in patients with PAI. Curiously, hyperkalemia was not a prominent feature. (6)

Other clinical characteristics include poor weight gain and salt craving. Adolescents may notice signs of decreased libido and loss of pubic and axillary hair. Usually, the clinical signs and symptoms are vague and can be confused with a viral gastroenteritis (nausea, vomiting, and abdominal pain) or depression.

Skin and mucosal hyperpigmentation raises the index of suspicion because hyperpigmentation is a classic finding and presents in more than 90% of patients with adrenal insufficiency. (52) The hyperpigmentation appears as a brownish coloration of the oral mucosa (eg, gums, lips, and inside cheeks), skin creases (eg, hands), scars, areola, and genitalia. The hyperpigmentation results from increased secretion of melanocyte stimulation hormone that derives from increased pro-opiomelanocortin production along with increased ACTH. (43)

Unrecognized and untreated patients can develop fatal adrenal crisis characterized by sudden sharp leg pain, lower back or abdominal pain, nausea, vomiting, hyponatremic dehydration, hyperkalemia, metabolic acidosis, hypotension, hypoglycemia, shock, or sudden death. (49)

DIAGNOSIS OF ADRENAL INSUFFICIENCY

The diagnosis of adrenal insufficiency requires an exquisite analysis of a patient's clinical presentation and biochemical profile. Any patient with vascular tone insufficiency (hypotension), shock that is unresponsive to initial resuscitation, and/or an abnormal electrolyte profile (low sodium or high potassium level, low glucose level, or metabolic acidosis) should be considered to have adrenal insufficiency until proven otherwise.

The initial screening on suspicion should include the measurement of early morning cortisol; ACTH can be added to assess the HPA axis. Increased plasmatic ACTH levels (>100 pg/mL [>22 pmol/L]) and a proportionally low serum cortisol concentration (<10 μg/dL [<275.9 nmol/L]) strongly raises the suspicion of glucocorticoid deficiency.

However, in the setting of diagnostic uncertainty, the biochemical diagnosis of adrenal insufficiency is made by an adrenal stimulation test with exogenous synthetic ACTH. There is considerable discussion regarding the best way to perform this test, specifically, choosing the best dose of ACTH that should be administered. Although most commonly it is a pediatric endocrinologist who orders this test, general pediatricians with previous expertise or with the resources for a technically appropriate test performance (eg, adequate laboratory setting) can also order it. Usually,

the situation where this test is needed happens most commonly with hospitalized patients; therefore, the test is most commonly performed in an inpatient setting. However, the test can also be performed as an outpatient procedure if there are appropriate laboratory resources (eg, formal nursing personnel and protocols in place to administer the medication and close contact with the prescriber physician to initiate the adequate treatment supplementation). Most medical centers administer high-dose ACTH (250 mg) as an intravenous injection. Serum cortisol is measured immediately before the injection and then 30 and 60 minutes after the injection. A normal physiologic response is an increase in the serum cortisol levels to a peak of at least 18 μg/dL (500 nmol/L) or higher after 60 minutes. Adrenal insufficiency is confirmed if the cortisol response is subnormal, especially in the setting of stress. (33)(39)(53)

For the diagnosis of PAI vs secondary adrenal insufficiency, the plasma ACTH measurement is useful because it is elevated in Addison disease and normal or low in secondary adrenal failure. Other tests for determining PAI vs secondary adrenal insufficiency are the metyrapone test and the insulin tolerance test. (43)

There is a fraction (approximately 10%) of total serum cortisol that is free (not bound to corticosteroid-binding globulin) and biologically active; the measurement of the free fraction (along with or instead of the total cortisol) may provide a more genuine assessment of the underlying cortisol physiologic features, especially in patients with secondary adrenal insufficiency. Of note, measuring salivary (also free) cortisol has similar efficacy but is not better than measuring serum (total) cortisol. However, these tests are increasingly unavailable at many centers. (5) Once the diagnosis of adrenal insufficiency is confirmed, a workup should focus on cause because it may affect treatment and outcome.

Impaired steroidogenesis is often suspected in newborns with ambiguous genitalia or elevated 17-hydroxyprogesterone levels on a newborn screen. A subsequent basal 17-hydroxyprogesterone measurement and 17-hydroxyprogesterone measurement after ACTH stimulation help confirm a CAH diagnosis (Figure 2).

The nonclassic CAH forms are more reliably diagnosed by their response to ACTH stimulation; random 17-hydroxyprogesterone measurements may be normal in mildly affected patients unless performed in the early morning. (54)

A differentiation of 21-hydroxylase deficiency from other enzymatic defects that cause CAH can be accomplished by evaluating the clinical features and by comparing precursor to product ratio of adrenocortical hormone profile after ACTH stimulation; both help highlight the underlying enzyme defect. (9)

CYP21 analysis is not essential for diagnosing CAH but aids in genetic counseling and helps to establish the diagnosis in uncertain cases and to identify mild forms. (14)(15)

If autoimmune adrenal insufficiency is suspected, a search for clinical and subclinical manifestations of other autoimmune disorders is warranted (eg, thyrotropin, glucose or hemoglobin A_{1c}, celiac panel, calcium and phosphorus, and parathyroid hormone). The best marker for autoimmune adrenalitis is high circulating 21-hydroxylase antibodies, which are present in 80% of cases. (55)

The presence of adrenal cortex autoantibodies in patients with polyglandular syndrome type 1 has a predictive value for the development of adrenal insufficiency in 92% of patients. (56) If concomitant hypogonadism is suspected (eg, menstrual disorders and loss or lack of pubic or axillary hair), measurement of gonadotropins (luteinizing hormone and follicle-stimulating hormone) with estradiol level in females and testosterone level in males is helpful to make the diagnosis of hypergonadotropic hypogonadism. (49)

X-linked ALD should be suspected in all boys presenting with progressive spastic paresis of unknown cause or with a typical cerebral demyelination pattern in brain imaging. Measurement of plasma very long-chain fatty acids continues to be the best initial test to make the X-linked ALD diagnosis. The amount of C26:0, the C24:0/C22:0 ratio, and the C26:0/C22:0 ratio should be analyzed. Heterozygous women with X-linked ALD often have high levels of plasma very long-chain fatty acids. Mutation analysis helps to identify *ABCD1* mutation for women with heterozygous X-linked ALD with normal very long-chain fatty acid levels in approximately 20% of cases. Prenatal screening diagnosis to detect a possible affected male fetus can be offered to women with heterozygous X-linked ALD who have been clearly confirmed by genetic analysis of the *ABCD1* gene. (23)

TREATMENT

Supplemental Stress Corticosteroid Dosing

The treatment of acquired adrenal insufficiency does not differ from the treatment for PAI. The use of stress corticosteroid dosing in situations of high stress after HPA axis suppression is paramount; however, data are lacking on how long patients should receive stress doses (the general recommendation is to provide stress corticosteroid dosing for the first 6–12 months after corticosteroid therapy discontinuation during periods of stress). In a study of infants treated with long-term corticosteroids (12–25 weeks of therapy), HPA function recovered within 6 to 12 weeks, a much

shorter time than the recommended period of stress dosing. (57)

Although a recent Cochrane review did not favor a specific recommendation regarding stress corticosteroid supplementation in surgical patients, (58) the general consensus is to supplement with a physiologic suppressive dose of corticosteroids according to the degree of surgical stress intensity. (47)(59) Is seems reasonable to supplement approximately 3 times the physiologic requirements for episodes of significant physiologic stress (as in surgery); however, in simple episodes of stress (mild upper respiratory tract infections, otitis media, or after immunizations), there is no need to provide supplementation. Table 2 provides recommendation for supplementation according to stress level. (59) The therapy should be guided as well by the clinical features (patient's perception of well-being, growth parameters, and vital signs). (60)

Treatment of Adrenal Crisis or Acute Adrenal Insufficiency

Acute adrenal insufficiency is a life-threatening condition, and, if clinically suspected, acute emergency treatment should be initiated. (61) The initial response is to provide hemodynamic resuscitation with intravenous fluids (20-mL/kg normal saline bolus), understanding that repeated boluses may be required before the initiation of maintenance fluids (isotonic crystalloids containing dextrose, usually 5% dextrose with normal saline) at a rate of 1.5 to 2 times the maintenance requirement. In addition to administering intravenous fluids, stress doses of hydrocortisone (100 mg/m² per day) should be administered as early as possible.

Patients with acute adrenal insufficiency should ideally be treated in an intensive care setting with continuous hemodynamic monitoring (or at least central venous pressure monitoring) to guide fluid resuscitation, continuous electrolyte supplementation (sodium or potassium), glucose monitoring, potential use of vasopressors (which can be by itself ineffective in untreated adrenal insufficiency), and administration of higher doses of dextrose and possibly systemic antibiotics if invasive meningococcemia is suspected. Potassium levels should be closely monitored because these patients may have severe hyperkalemia secondary to mineralocorticoid deficiency. Treating hyperkalemia requires increasing potassium excretion (use of cationic resins [sodium polystyrene] and loop diuretics), stabilizing the cell membrane (intravenous calcium), and promoting cellular shifting of potassium (use of insulin or dextrose, bicarbonate, and inhaled albuterol). (49)

For patients who use long-term mineralocorticoid supplementation (fludrocortisone), this supplementation can be discontinued while using hydrocortisone at stress doses. Approximately 20 mg of intravenous hydrocortisone has a mineralocorticoid activity equivalent to 0.1 mg of fludrocortisone, providing adequate mineralocorticoid supplementation. (27)

Long-Term Treatment of Adrenal Insufficiency

The long-term treatment of adrenal insufficiency consists of exogenous corticosteroid replacement (both glucocorticoid and mineralocorticoid) along with the evaluation and treatment of coexistent hormonal deficiencies, especially thyroid hormone. Adrenal insufficiency must be treated before initiating thyroid hormone replacement therapy to prevent the development of an adrenal crisis. For children, the preferred cortisol replacement is oral hydrocortisone (10–20 mg/m² per day divided into 3 doses) because of its short half-life and

TABLE 2. Recommendation for Corticosteroid Supplementation According to Stress Level[a]

LEVEL OF STRESS	RECOMMENDATION
Minimal (mild upper respiratory tract infection, nonfebrile infections)	No need to supplement
Minor stress (superficial hernia surgery, ocular surgery)	Corticosteroid dose equivalent to 25 mg of intravenous hydrocortisone succinate on induction of anesthesia (single dose)
Moderate stress (orthopedic surgery, cholecystectomy)	Corticosteroid dose equivalent to 50 mg of intravenous hydrocortisone succinate on induction of anesthesia and then 25 mg every 8 hours for a total of 24 hours
Major stress (large digestive surgery, cardiovascular surgery)	Corticosteroid dose equivalent to 100 mg of intravenous hydrocortisone succinate starting 2 hours before intervention and then 50 mg every 8 hours for 24 hours, then 25 mg every 8 hours for 24-48 hours

[a]Adapted from Luca et al. (46) The doses are total full doses.

minimal suppression of growth. The mineralocorticoid replacement is performed with fludrocortisone at a dose of 0.1 to 0.2 mg/d. Sodium chloride supplementation may be required in neonates and infants. (27)

Patients who use or have used corticosteroids for long periods (>3 weeks per year in the previous year) must be educated on their risk of developing acute adrenal insufficiency in the setting of stress conditions. Generally, doubling the current dose of oral hydrocortisone should be sufficient in most patients when exposed to acute stress (eg, diarrheal illnesses, severe systemic infections, trauma, burns, and surgery) for a period of 24 to 48 hours. If oral hydrocortisone formulation cannot be used, then parenteral hydrocortisone must be administered (intravenous or intramuscular dose of 50 mg/m²) every 8 hours.

The use of mineralocorticoid replacement is required in salt-losing CAH. Fludrocortisone (9α-fluorocortisol) is the only mineralocorticoid currently available and requires enteral administration. The mineralocorticoid sensitivity increases with age; therefore, although newborns with CAH may require up to 0.4 mg of fludrocortisone daily, the usual replacement dose an adult patient requires is 0.05 to 0.1 mg/d. In addition, patients with salt-losing CAH require sodium

chloride supplementation to allow for sodium to be reabsorbed at the nephron level. (27) The clinician needs to be aware of the glucocorticoid and mineralocorticoid potency and equivalence of the different available corticosteroid preparations (Table 3).

SUMMARY

Adrenal insufficiency is a life-threatening condition. (4) In infants, the most common cause is CAH. On the basis of expert consensus, universal screening of all newborns is performed worldwide to avoid the fatality and misdiagnosis of the classic salt-wasting form of CAH. (14)

Strong research evidence indicates that long-term corticosteroid use is consistently associated with acquired adrenal insufficiency. Clinical studies have found that all types of corticosteroid administration (injectable [intravenous, intramuscular, or subcutaneous], intranasal, inhaled, and topical mucocutaneous) cause HPA axis suppression with consequent acute adrenal insufficiency during periods of stress (eg, surgery, burns, and critical illness). (33)(34)

Research evidence and clinical consensus recommend measurement of early morning cortisol as the initial diagnostic

TABLE 3. **Equivalence of Therapeutic Corticosteroids**[a]

CORTICOSTEROID	ANTI-INFLAMMATORY GLUCOCORTICOID EFFECT	GROWTH-RETARDING GLUCOCORTICOID EFFECT	SALT-RETAINING MINERALOCORTICOID EFFECT	PLASMA HALF-LIFE, MIN	BIOLOGIC HALF-LIFE, H
Cortisol (hydrocortisone)	1.0	1.0	1.0	80–120	8
Cortisone acetate (oral)	0.8	0.8	0.8	80–120	8
Cortisone acetate (intramuscular)	0.8	1.3	0.8		18
Prednisone	4	5	0.25	200	16–36
Prednisolone	4		0.25	120–300	16–36
Methylprednisolone	5	7.5	0.4		
Betamethasone	25		0	130–330	
Triamcinolone	5		0		
Dexamethasone	30	80	0	150–300	36–54
9α-Fludrocortisone	15		200		
DOC acetate	0		20		
Aldosterone	0.3		200–1000		

DOC acetate = deoxycorticosterone acetate.
[a]Adapted from Miller and Fluck. (28) The way to interpret this table for dosing purposes is as follows: for example, prednisone has 4 times the cortisol glucocorticoid effect; therefore, 1 mg of prednisone is equivalent to 4 mg of hydrocortisone and 5 mg of prednisone is equivalent to 20 mg of hydrocortisone; dexamethasone has 30 times the cortisol glucocorticoid effect; therefore, 1 mg of dexamethasone is equivalent to 30 mg of hydrocortisone.

screening test if adrenal insufficiency is suspected. However, in the setting of diagnostic uncertainty, the biochemical diagnosis is made by an adrenal stimulation test with exogenous synthetic ACTH. Adrenal insufficiency is confirmed if the response is subnormal, especially in the setting of stress. (44)(45)(46)(47)(48)

Acute adrenal insufficiency is a life-threatening condition, and, if suspected, immediate emergency treatment should be initiated mainly with fluid resuscitation and intravenous hydrocortisone. (4) The clinician must provide stress corticosteroid supplementation in situations of high stress when there are risk factors for HPA axis suppression. Data are lacking on how long patients should receive stress doses. On the basis of clinical consensus, the general recommendation is to provide stress corticosteroid doses for the first 6 to 12 months after corticosteroid therapy discontinuation during periods of stress. (47)(57)(58)(59)

References for this article are at http://pedsinreview.aappublications. org/content/36/3/92.full.

Parent Resources from the AAP at HealthyChildren.org

- http://www.healthychildren.org/english/health-issues/conditions/genitourinary-tract/pages/explaining-disorders-of-sex-development-intersexuality.aspx

PIR Quiz

1. Fraternal twins, a girl and a boy, were both born with the salt-wasting form of congenital adrenal hyperplasia. Given the same diagnosis, why is the diagnosis of the infant girl more likely to be detected earlier than her brother?
   - A. Genital ambiguity.
   - B. Higher adrenocorticotropic hormone (ACTH) levels.
   - C. Hyperpigmentation.
   - D. More severe hypernatremia.
   - E. The absence of hyperkalemia.

2. A 6-year-old girl presents with unrelenting, uncharacteristic fatigue. A biochemical workup suggests adrenal insufficiency. An elevation of which of the following would suggest primary adrenal insufficiency?
   - A. ACTH.
   - B. Blood urea nitrogen.
   - C. Glucose.
   - D. Sodium.
   - E. Cortisol.

3. In a 1-month-old infant with ambiguous genitalia, congenital adrenal hyperplasia is suspected if the following biochemical component is elevated:
   - A. Cholesterol.
   - B. Serum aldosterone.
   - C. Serum cortisol.
   - D. 17-Hydroxyprogesterone.
   - E. 21-Hydroxylase antibodies.

4. A 14-year-old boy with chronic asthma had been treated with very high-dose inhaled corticosteroids. His asthma has improved, and use of inhaled corticosteroids was discontinued. His physician has concerns regarding adrenal insufficiency from intercurrent stress due to illness, trauma, or surgery. The duration during which stress doses of glucocorticoids are generally recommended after discontinuation of long-term corticosteroid use is:
   - A. 14 days.
   - B. 1 month.
   - C. 3 months.
   - D. 6 to 12 months.
   - E. 2 years.

5. A 3-year-old girl is diagnosed as having adrenal insufficiency. Among the following, the preferred cortisol replacement is:
   - A. Aldosterone.
   - B. Dexamethasone.
   - C. Hydrocortisone.
   - D. Methylprednisolone.
   - E. Prednisone.