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Adrenal Insufficiency: Still a Cause of Morbidity and Death in Childhood

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ABSTRACT

Adrenal insufficiency is relatively rare in childhood and adolescence. Signs and symptoms may be nonspecific; therefore, the diagnosis may not be suspected early in the course. If unrecognized, adrenal insufficiency may present with life-threatening cardiovascular collapse. Adrenal crisis continues to occur in children with known primary or secondary adrenal insufficiency during intercurrent illness because of failure to increase glucocorticoid dosage. In this article, current knowledge of the incidence, diagnosis, and treatment of adrenal insufficiency in children and factors precipitating adrenal crisis are summarized. Suggestions for prevention of adrenal crisis in patients at risk are provided for health care professionals and families.

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Key Words

adrenal disorders, morbidity/mortality, adverse outcomes

Abbreviations

CRH—corticotropin-releasing hormone
ACTH—adrenocorticotropic hormone
CAH—congenital adrenal hyperplasia
GH—growth hormone

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THOMAS ADDISON¹ first identified a syndrome characterized by wasting and hyperpigmentation associated with adrenal gland destruction 150 years ago. Life-saving glucocorticoid replacement has been available to treat adrenal insufficiency for >50 years. The most common cause of acute adrenal insufficiency in North America today is glucocorticoid withdrawal or omission in patients being treated with chronic pharmacologic doses.² Although there have been significant advances in understanding the molecular genetics of congenital and acquired causes of adrenal insufficiency in the pediatric population, the clinical diagnosis is frequently delayed or missed because of its vague and nonspecific symptoms early in the course. If unrecognized, adrenal insufficiency may present as a life-threatening crisis with acute cardiovascular collapse. A recent survey of adult patients with adrenal insufficiency who are members of the National Adrenal Disease Foundation reported that 60% had sought the advice of ≥ 2 physicians before the diagnosis was made.³ In 5 of 16 children in Melbourne, Australia, diagnosed with primary adrenal insufficiency over a 10-year period, there was a median of 2 years' delay between the onset of the first symptoms and the diagnosis.⁴ Four of the remaining 11 children presented in adrenal crisis. Once the diagnosis of adrenal insufficiency is established, continuing reminders to patients, families, and medical personnel regarding the need for higher doses of glucocorticoid replacement during intercurrent illness and surgery are required. Failure to increase glucocorticoid supplementation during physical stress remains a significant cause of morbidity and mortality for these patients.

ETIOLOGY AND INCIDENCE

Adrenal insufficiency may be categorized as primary or secondary and congenital or acquired. In primary adrenal insufficiency, glucocorticoid and, frequently, mineralocorticoid hormones are lost. In secondary adrenocortical insufficiency there is lack of corticotropin-releasing hormone (CRH) secretion from the hypothalamus and/or adrenocorticotrophic hormone (ACTH) secretion from the pituitary, which results in hypofunction of the adrenal cortex. In secondary adrenal insufficiency mineralocorticoid function is preserved. Causes of adrenal insufficiency in children and adolescents are listed in Table 1. For a more comprehensive review of clinical, biochemical, and genetic characteristics of specific etiologies, see refs 3, 5, and 6.

Primary Adrenal Insufficiency

Primary adrenal insufficiency is uncommon in the Western population and is estimated to affect 90 to 140 per 1 million people.² In adults, >80% of cases are caused by autoimmune adrenal destruction, which is most common in women aged 25 to 45 years but can occur in both genders at any age. Glandular infiltration by tuberculosis

is the second most common etiology worldwide. Perry et al⁶ recently reported their experience with primary adrenal insufficiency in children ≤ 18 years old in Montreal, Canada, over the past 20 years. Of the 103 patients identified, 72% were diagnosed with congenital adrenal hyperplasia (CAH), 13% had autoimmune adrenal insufficiency, and the remaining 15% had adrenoleukodystrophy, syndromes (Wolman, Triple A [adrenal insufficiency, achalasia, alacrima], Zellweger), or unexplained adrenal insufficiency. An etiology for primary adrenal insufficiency was identified in 94% of cases. In a study performed in Melbourne, Australia,⁴ in which only non-CAH primary adrenal insufficiency was reported, there were 5 cases each of autoimmune adrenal insufficiency, adrenoleukodystrophy, and adrenal hypoplasia congenita and 1 case of the IMAGE syndrome (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies).

Data regarding mortality rates in patients with primary adrenal insufficiency are scarce. CAH is the most common form of primary adrenal insufficiency in children, with an incidence of 1 in 10 000 to 18 000 live births.⁷ Clinically, girls are most often identified at birth because of virilized genitalia, whereas boys are usually diagnosed after they present with a salt-wasting crisis at 2 to 3 weeks of age. The most common enzyme deficiency is 21-hydroxylase. Mortality rates in the neonatal period resulting from missed diagnosis (primarily boys) are not readily available. However, in a review of children diagnosed with CAH between 1969 and 1998 in middle Europe, it was estimated that ~ 2 to 3 undiagnosed subjects per year died in the neonatal period.⁸ These data were based on the finding of fewer total boys diagnosed with CAH over this time period, when the ratio should have been 1:1. Mortality in the first year of life after making the diagnosis was reported to be 5 times higher than in the general population; this improved over the last decade of the observation period. A British study estimated a fourfold increase in mortality in children with CAH in the first 4 years of life over a similar period of observation.⁹ Because of delayed or missed diagnosis in affected male infants (and some very virilized female infants), in 2002 the Joint Lawson Wilkins Pediatric Endocrine Society/European Society for Pediatric Endocrinology Working Group recommended biochemical screening for CAH in the newborn period.¹⁰ The majority of states in the United States are currently performing newborn screening, as are many other countries. Infant screening programs have markedly decreased the time to diagnosis, theoretically decreasing morbidity. Compared with retrospective studies in which the incidence in female infants was reported to be greater than that of males, in states where infant screening has been implemented, the incidence of salt-wasting CAH in boys and girls seems to be equal, suggesting that screening has impacted mortality rates as

TABLE 1 Causes of Glucocorticoid Deficiency

| Condition | Affected Gene | Clinical Phenotype |
|---|-----------------------------|--|
| Primary | | |
| Congenital | | |
| CAH | | |
| 21-hydroxylase deficiency | <i>CYP21</i> | Virilization/salt-wasting |
| 3- β -hydroxysteroid dehydrogenase deficiency | <i>HSD3B2</i> | Ambiguous genitalia/salt-wasting |
| 11- β -hydroxylase deficiency | <i>CYP11B2</i> | Virilization/hypertension (not infants) |
| Cholesterol desmolase deficiency | <i>CYP11A</i> | XY sex reversal/salt-wasting |
| Lipoid hyperplasia | <i>STAR</i> | XY sex reversal/salt-wasting |
| Congenital adrenal hypoplasia | <i>SF-1</i> <i>DAX-1</i> | XY sex reversal Hypogonadotropic hypogonadism IMAGE syndrome (intrauterine growth retardation, metaphyseal dysplasia, genital anomalies) |
| Triple A or Allgrove | <i>AAAS</i> | Achalasia, alacrima |
| ACTH resistance | <i>MC2R, MRAP</i> | |
| Glucocorticoid resistance | <i>GCCR</i> | Mineralocorticoid/androgen excess |
| Metabolic diseases | | |
| Adrenoleukodystrophy | <i>ABCD1</i> | Neurologic deterioration |
| Zellweger | <i>PEX</i> | Cerebrohepato renal syndrome |
| Smith-Lemli-Opitz | <i>DCHR7</i> | Polydactyly, XY sex reversal, mental retardation |
| Wolman disease | <i>LIPA</i> | Hepatomegaly |
| Mitochondrial disease | | |
| Kearns-Sayre syndrome | | Ophthalmoplegia, myopathy |
| Acquired | | |
| Autoimmune adrenalitis | | |
| Isolated | | |
| Autoimmune polyendocrinopathy syndrome type 1 | <i>AIRE</i> | |
| Autoimmune polyendocrinopathy syndrome type 2 | | |
| Hemorrhage/infarction | | |
| Trauma | | |
| Waterhouse-Frederickson syndrome | | |
| Anticoagulation | | |
| Drug effects | | |
| Aminoglutethimide, mitotane, ketoconazole, metyrapone, medroxyprogesterone, megestrol, etomidate, rifampin, phenytoin, barbiturates | | |
| Infection | | |
| Viral: HIV, cytomegalovirus | | |
| Fungal: coccidiomycosis, histoplasmosis, blastomycosis, cryptococcosis | | |
| Mycobacterial: tuberculosis | | |
| Amebic | | |
| Infiltrative | | |
| Hemochromatosis, histiocytosis, sarcoidosis, amyloidosis, neoplasm | | |
| Secondary | | |
| Hypothalamus | | |
| Congenital | | |
| Septo-optic dysplasia | <i>HESX1</i> | Nystagmus |
| CRH deficiency | | |
| Maternal hypercortisolemia | | |
| Acquired | | |
| Steroid withdrawal after prolonged administration | | |
| Inflammatory disorders | | |
| Trauma | | |
| Radiation therapy | | |
| Surgery | | |
| Tumors | | |
| Infiltrative disease: sarcoidosis, histiocytosis X | | |
| Pituitary | | |
| Congenital | | |
| Aplasia/hypoplasia | | |
| Multiple anterior pituitary hormone deficiencies | | |
| Isolated ACTH deficiency | <i>PROP1</i> <i>TPIT</i> | |
| Proprotein convertase 1 | <i>POMC</i> <i>PCSK1</i> | Obesity, red hair Hypoglycemia, malabsorption, gonadotropin deficiency |
| Acquired | | |
| Steroid withdrawal after prolonged administration | | |
| Trauma | | |
| Tumor: craniopharyngioma | | |
| Radiation therapy | | |
| Lymphocytic hypophysitis | | |

well.⁷ In Quebec, Canada, the male/female ratio of neonates diagnosed with CAH is 1:1 despite the absence of screening, suggesting that with a high level of clinical awareness this diagnosis can be made without a formal screening program.⁶ The high false-positive rate, particularly in premature infants, has prevented universal adoption of biochemical screening for CAH.¹¹ Prenatal diagnosis is now possible for pregnancies at high risk.¹²

Arlt and Allollo² reported the risk of adrenal crisis in 53 adult patients with adrenal insufficiency to be higher in primary adrenal insufficiency (3.8 admissions per 100 patient-years) compared with secondary adrenal insufficiency (2.5 per 100 patient-years).

Secondary Adrenal Insufficiency

Secondary adrenal insufficiency is much more frequent and has an estimated prevalence of 150 to 280 per 1 million people.² Secondary adrenal insufficiency caused by abrupt discontinuation of glucocorticoid therapy or stress while on suppressive doses is the most common cause because of the widespread use of exogenous steroids for a variety of disorders. The rate of adrenal crisis or death is unknown. Pharmacologic doses of glucocorticoids administered orally, intramuscularly, intranasally, inhaled, transdermally, or intraorbitally may result in suppression of the hypothalamic-pituitary-adrenal axis. Treatment courses for as brief as 2 weeks may result in transient suppression of endogenous cortisol production.⁵ In a study of children being treated for leukemia, a 4-week course of glucocorticoids resulted in suppression of the hypothalamic pituitary axis for up to 8 weeks after discontinuation.¹³ Prolonged therapy may result in suppression for 6 to 9 months.¹⁴ Disease of the hypothalamic-pituitary axis must also be considered in patients with secondary adrenal insufficiency (Table 1). Most secondary adrenal insufficiency that is not associated with withdrawal of pharmacologic glucocorticoid therapy occurs together with other pituitary hormone deficiencies and either a history of pituitary insult or anatomic abnormality of the hypothalamic-pituitary axis evident on MRI.¹⁵

Mortality data in children with secondary adrenal insufficiency come primarily from recent reports regarding follow-up of individuals treated with pituitary growth hormone (GH). These reports include primarily children with hypothalamic-pituitary disease. Three articles have reported a three- to fourfold increase in mortality compared with the general population in children treated with pituitary GH from the 1960s and followed to the 1990s in England, Canada, and the United States.^{16–18} Of all the deaths, 12% to 25% were a result of hypoglycemia and/or secondary adrenal insufficiency. These preventable deaths were seen in individuals of all ages and were associated with a variety of causes of hypopituitarism. In the US experience, 24% of all the deaths were sudden and unexpected.¹⁸ Of these, 74%

were said to occur in individuals with known multiple pituitary hormone deficiencies; in a third, death was associated with an intercurrent illness. In the opinion of the study's authors, roughly half of the group with sudden and unexplained death had a clinical course suggestive of adrenal insufficiency. Children <2 years of age with GH deficiency and hypoglycemia (and most likely severe adrenal insufficiency) were one of the highest-risk groups (mortality increased 10-fold). The death rate in the children with a history of hypoglycemia who were <6 years of age was 1 per 31 to 54 patient-years. After 6 years of age, the death rate resulting from secondary adrenal insufficiency declined slightly but remained fairly constant with advancing age (1 per 113–173 person-years). In general, children with idiopathic, isolated GH deficiency did not have increased mortality.

There are few data regarding death or hospitalization in children without hypothalamic-pituitary disease who develop secondary adrenal insufficiency caused by withdrawal of pharmacologic glucocorticoid therapy. In a report of 2900 surveys mailed to consultant pediatricians and adult endocrinologists in the United Kingdom regarding adrenal insufficiency after the use of inhaled glucocorticoids, 23 children were reported to have acute hypoglycemia.¹⁹ Most had been using >500 μg of inhaled fluticasone daily. Linear growth rate does not predict which children will have adrenal suppression on inhaled glucocorticoids.²⁰

PHYSIOLOGIC EFFECTS OF GLUCOCORTICOIDS ON BLOOD GLUCOSE AND BLOOD PRESSURE

Glucocorticoids have effects on all body tissues. The overall metabolic action of glucocorticoids is catabolic, promoting protein and lipid breakdown and restraining protein synthesis in muscle, connective tissue, adipose tissue, and lymphoid cells. The effects of cortisol are antagonistic to those of insulin, increasing the concentration of glucose by stimulating gluconeogenesis. Cortisol decreases glucose use by muscle and promotes lipolysis in adipose tissue. Amino acids and glycerol released by the catabolic action of cortisol on protein and fat are used as gluconeogenic substrates. The net effect is increased production and conservation of glucose for use by essential tissues, such as the brain and red blood cells, at the expense of less essential tissues during times of stress or starvation.^{5,14}

Cortisol contributes to the maintenance of normal blood pressure through several mechanisms. Under non-stressful conditions, cortisol increases urine flow by stimulating glomerular filtration rate and decreasing water resorption; however, at high concentrations, cortisol can act like a mineralocorticoid, promoting sodium and water retention. In high concentration, cortisol increases angiotensinogen synthesis by the liver and increases the vascular reactivity to vasoconstrictors. In the adrenal medulla, cortisol is required for the enzymatic activity of

phenylethanolamine *N*-methyltransferase, which converts norepinephrine to epinephrine. Epinephrine stimulates cardiac output as well as hepatic glucose production. Cortisol decreases capillary permeability and decreases the production and activity of nitrous oxide and the vasodilatory kinin and prostaglandin systems during stress, preventing life-threatening hypotension.¹⁴

PHYSIOLOGIC EFFECTS OF ALDOSTERONE

Aldosterone is produced in the zona glomerulosa and is controlled primarily by the renin-angiotensin system, serum potassium, and ACTH. Under normal circumstances the renin-angiotensin system predominates. The primary target of aldosterone is the kidney, where it stimulates reabsorption of sodium and secretion of potassium and hydrogen ions. Aldosterone deficiency results in hyperreninemia, hyperkalemia, hyponatremia, and mild acidosis.

SIGNS AND SYMPTOMS OF ADRENAL INSUFFICIENCY

Patients with acute adrenal insufficiency generally present with acute dehydration, hypotension, hypoglycemia, or altered mental status. Acute adrenal insufficiency may be triggered by infection or trauma but may also be seen without an obvious concomitant illness or stress. Hypoglycemia is most common in young children. Altered mental status may occur at any age with or without hypoglycemia.²¹

Patients with chronic adrenal insufficiency usually complain of chronic fatigue, anorexia, nausea, vomiting, loss of appetite, weight loss, and recurring abdominal pain. Symptoms may mimic gastrointestinal illness or psychiatric disorder, in particular, behavior changes or depression. Although increased skin pigmentation may be noted because of elevation of pro-opiomelanocortin and melanocyte-stimulating hormone, a ligand derived from pro-opiomelanocortin that causes hyperpigmentation of melanin-containing skin cells and suppresses appetite,⁵ it is not always clinically obvious. Salt craving is common in chronic primary adrenal insufficiency. Hyperpigmentation and salt craving are not observed in patients with secondary adrenal insufficiency.

Unless there is a history of recent pharmacologic glucocorticoid therapy, secondary adrenal insufficiency is usually associated with signs of other pituitary hormone deficiencies such as growth failure, delayed puberty, secondary hypothyroidism, and/or diabetes insipidus (polyuria and polydipsia).

Physical Clues

In chronic primary adrenal insufficiency, increased skin pigmentation may be observed, particularly in areolae, genitalia, scars, and moles. Areas unexposed to sun (eg, palmer creases, axillae) often are hyperpigmented. The patient also may have pigmentary lines in the gums. If not frankly hypotensive, the patient may demonstrate

orthostatic hypotension. Some patients also may lose pubic and axillary hair because adrenal androgens support growth of body hair in these areas.

Laboratory Findings

Hyponatremia and hyperkalemia are common in primary adrenal insufficiency because of deficient aldosterone secretion. Hypoglycemia is common in both primary and secondary adrenal insufficiency. Hyponatremia may also be seen in secondary adrenal insufficiency because of water retention from lack of cortisol to antagonize the effect of vasopressin secretion.¹⁴

The diagnosis of primary adrenal insufficiency is confirmed by documentation of an elevated plasma ACTH level (frequently >100 pg/mL) and a low serum cortisol level (generally <10 µg/dL). If there is some question about the diagnosis, an ACTH-stimulation test (250 µg or 15 µg/kg for infants <2 years, intravenously) can be conducted; if there is primary adrenal insufficiency, there will be a subnormal peak cortisol level (<18 µg/dL) 60 minutes after ACTH administration. Mineralocorticoid deficiency can be confirmed with the finding of relatively low aldosterone levels in the face of hyperreninemia, with or without hyponatremia and/or hyperkalemia.

The diagnosis of secondary adrenal insufficiency is associated with low blood cortisol and ACTH levels. An 0800-hour cortisol level of <3 µg/dL is suggestive of the diagnosis; a value ≥18 µg/dL essentially eliminates it. Confirmation of hypothalamic-pituitary-adrenal insufficiency may be more difficult than primary adrenal insufficiency. The gold-standard test mimicking severe stress has traditionally been insulin-induced hypoglycemia (serum cortisol measured 60 minutes after 0.05–0.15 U/kg of intravenous regular insulin, assuming drop in glucose 50% from baseline or <45 mg/dL; reference cortisol response: ≥18 µg/dL). This test must be performed cautiously under experienced medical supervision. Many centers are no longer using this test because of the risk of hypoglycemic seizure and severe hypokalemia after treatment with glucose infusion.²² Other available tests include stimulation with CRH (1 µg/kg intravenously over 2 minutes; reference response: two-fold increase in ACTH level at 15 minutes and three- to fourfold increase in cortisol levels at 13–30 minutes), a low (1 µg intravenously) or standard (250 µg intravenously) dose of ACTH (reference cortisol response: ≥18 µg/dL 30–60 minutes later), and glucagon 0.1 mg/kg subcutaneously or intramuscularly (between 2 and 3 hours later, cortisol rises to ≥14 µg/dL as glucose falls, monitoring every 15 minutes during the hour).²³ The low-dose (1 µg) ACTH test seems to be more sensitive than the standard dose in the setting of secondary adrenal insufficiency.²⁴ A recent report from Germany suggests that glucagon may be a reasonably sensitive test of hypothalamic-pituitary-adrenal function that is easy to

administer and is not associated with the risks associated with insulin-induced hypoglycemia.²³ Metyrapone (30 mg/kg orally at midnight) inhibits 11-hydroxylase, the final step in cortisol synthesis, thereby decreasing cortisol feedback on ACTH; the following morning 11-deoxycortisol level is $>5 \mu\text{g/dL}$ in "normal" children.⁵ This is a cumbersome test that is rarely performed because of the difficulty in obtaining metyrapone and the risk of precipitating an adrenal crisis. In the neonate, a critical venous sample should be drawn at the time of hypoglycemia and evaluated for glucose, cortisol, GH, and insulin levels. Results may guide the need for further evaluation for multiple pituitary hormone deficiencies, isolated ACTH deficiency, or primary adrenal insufficiency.

Glucocorticoid resistance, a rare entity that is associated with mutations in the gene encoding the glucocorticoid receptor, is associated with elevated levels of ACTH, increased urinary free cortisol excretion, and increased production of mineralocorticoids and/or adrenal androgens.²⁵

TREATMENT OF ACUTE ADRENAL INSUFFICIENCY

In the hypotensive patient, rapid restoration of intravascular volume with isotonic sodium chloride containing dextrose is needed. Additional dextrose (D₂₅W) should be administered as required to treat hypoglycemia.

Blood should be drawn to test for cortisol, electrolyte, glucose, and ACTH levels, plasma renin activity, and aldosterone level. Measurement of urinary sodium and potassium concentrations may also be helpful in assessing mineralocorticoid status. Simultaneous with the administration of intravenous fluids, stress doses of glucocorticoid should be given. Hydrocortisone is the treatment of choice because of its mineralocorticoid activity. The recommended stress dose of hydrocortisone is 50 to 75 mg/m² intravenously initially, followed by 50 to 75 mg/m² per day intravenously divided in 4 doses.²¹ It should be recognized that recommendations for stress doses are empiric and not based on carefully controlled clinical trials. Hydrocortisone may be given intramuscularly if no intravenous access exists, but intramuscular administration works more slowly and may be ineffectively absorbed if peripheral perfusion is poor. Comparable stress doses are 10 to 15 mg/m² for methylprednisolone and 1.5 to 2 mg/m² for dexamethasone. The latter 2 corticosteroids have very little mineralocorticoid activity. Prednisone is not a glucocorticoid of choice, because it must be converted to prednisolone before it has glucocorticoid activity. In patients with liver failure, this conversion may be impaired.

Dexamethasone can be used if one wants to treat the patient urgently but wishes to carry out a diagnostic ACTH-stimulation test. Treatment should never be withheld if the diagnosis of adrenal insufficiency is suspected. If the patient has good gastrointestinal function, fludro-

cortisone (0.1 to 0.2 mg daily), a synthetic mineralocorticoid, may be administered orally. Usually, administration of intravenous sodium chloride along with large doses of hydrocortisone are sufficient to begin normalizing electrolyte abnormalities, making the addition of mineralocorticoid unnecessary in the first hours of treatment. Hydrocortisone has $\sim 1/400$ th the mineralocorticoid activity of fludrocortisone.² Very rarely, if there is a coexisting cardiomyopathy and/or acute renal failure prohibiting rapid rehydration, more aggressive therapy of hyperkalemia may be needed. When the patient has been stabilized, is feeling well, and is eating normally, glucocorticoid dosing may be tapered to physiologic replacement doses. In the first year of life, infants with primary adrenal insufficiency are generally supplemented with 1 to 2 g of sodium chloride to ensure adequate sodium intake.

Children with possible adrenal insufficiency should be referred to a pediatric endocrinologist for further diagnostic evaluation, follow-up care, and counseling.

Physiologic Replacement Doses of Glucocorticoid

Maintenance dosing of glucocorticoid for replacement therapy is based on the secretory rate of cortisol in the intact system. However, there is debate about the baseline secretory rate, which makes it difficult to determine an exact replacement regimen. There are data indicating that the secretory rate may be as low as 5 to 6 mg/m² per day without substantial variation with pubertal status.²⁶⁻²⁸ Because the bioavailability of cortisol is reduced by gastric acids and first pass in the liver, the usual maintenance dose for glucocorticoid replacement needs to be adjusted above the estimated secretion rate. Therefore, 9 to 12 mg/m² per day of oral hydrocortisone is probably a reasonable initial starting dose for individuals with primary adrenal insufficiency. Patients with secondary adrenal insufficiency, which is frequently partial, may do well on a lower dose. Adjustments are subsequently made on an individual basis to avert signs and symptoms of adrenal insufficiency while also avoiding the growth retardation and Cushingoid features that can accompany overreplacement.

Cortisol (hydrocortisone) is usually the drug of choice and is dosed every 8 hours; other preparations with longer half-lives (ie, prednisone, dexamethasone) can also be used if necessary to facilitate adherence. It is more difficult to finely adjust the dosage of these more potent synthetic preparations, and some have little or no activity at the mineralocorticoid receptor, which requires an increase in mineralocorticoid replacement. Although most replacement protocols call for dividing the cortisol equally either 3 times per day or every 8 hours, some favor skewing the dose slightly toward a higher proportion being administered in the morning to attempt to mimic the normal diurnal variation of cortisol in patients with adrenal insufficiency that does not stem

from CAH. In patients with CAH, there is evidence to suggest that nighttime cortisol clearance is reduced, suggesting that the hydrocortisone dose should be weighted to the morning time.²⁹ Nevertheless, some clinicians prefer to treat CAH with a higher dose of cortisol or a longer-acting glucocorticoid at night in an attempt to suppress the early-morning ACTH-mediated adrenal androgen production.

ACTH cannot be used as a criterion for glucocorticoid dose adjustment in primary adrenal insufficiency. Attempts at achieving ACTH levels within the reference range leads to chronic overreplacement. Rather, one should gauge the quantity and timing of glucocorticoids on the basis of the patient's own sense of well-being and energy level. Frequent headaches, lethargy, nausea, and/or abdominal pain may indicate inadequate treatment. Objective signs of inadequate replacement therapy are orthostatic pulse and/or blood pressure changes. If skin hyperpigmentation becomes apparent in primary adrenal insufficiency, obtaining plasma ACTH levels may be helpful.

Stress Dosing

The cortisol secretory rate increases substantially during physiologic stress. Consequently, all patients with adrenal insufficiency (primary or secondary) need to be educated about the need to increase their glucocorticoid dose during stress to avoid preventable episodes of adrenal crisis, which can be fatal. Patients should also be reminded to wear a medical alert bracelet or other jewelry item and to carry an emergency medical information card to ensure that medical providers know about their underlying disorder.

There is controversy as to what constitutes "stress" and the need to increase glucocorticoid doses. Mild stresses such as immunizations, uncomplicated viral illnesses, and upper respiratory tract infections with sore throat, rhinorrhea, and/or low-grade fever and otitis media may not require use of a stress-dose steroid regimen if the patient otherwise acts and appears well. More severe stresses such as illness accompanied by fever $\geq 38^{\circ}\text{C}$, vomiting, diarrhea, inadequate oral intake, lethargy, surgery, trauma, dental work, and large burns should be accompanied by increased glucocorticoid doses to prevent the hypoglycemia, hypotension, and even cardiovascular collapse that can occur in the setting of an adrenal crisis. Moderate-to-extreme physical exercise may be facilitated by a slight increase ($\sim 30\%$) in hydrocortisone dosage 60 minutes before exercise. This too, is controversial; Weise et al³⁰ recently reported that in adolescents with CAH, an additional morning dose of hydrocortisone, which resulted in doubling of cortisol levels, did not affect performance, nor did it alter blood glucose, lactate, free fatty acids, or epinephrine levels during short-term high-intensity exercise compared with placebo. Glucose and epinephrine levels during

exercise were significantly lower in patients with CAH compared with a healthy control group. This research study was performed under laboratory conditions and should not be interpreted to mean that patients with CAH should be exercise restricted. There are insufficient data as yet to draw such conclusions, and prevailing collective experience suggests that such patients are capable of vigorous physical activity without adverse consequences. In their consensus statement on CAH, the Lawson Wilkins Pediatric Endocrine Society and European Society for Paediatric Endocrinology did not recommend increasing the glucocorticoid dose during psychological and emotional stress.¹⁰

The degree to which doses should be increased is also debated, with recommendations varying between 2 and 10 times the maintenance rate.³¹ A common recommendation is to treat most stresses that require increased doses with hydrocortisone 30 to 50 mg/m² per day (approximately tripling the daily dose) divided into 3 or 4 doses over the day. It is important that each patient know his or her specific stress-dose regimen, because one might need to increase the maintenance dose more substantially for an individual who is on relatively low-dose maintenance replacement for secondary adrenal insufficiency compared with an individual on relatively larger doses needed to suppress excess androgen production in the treatment of CAH.

The most severe stresses, such as major surgery or sepsis, are often treated more aggressively, with doses up to 100 mg/m² per day divided every 6 hours intravenously. Although various glucocorticoid preparations could be used for stress dosing, hydrocortisone is the preferred agent because of its mineralocorticoid activity. In most instances, stress doses are administered for only 24 to 48 hours unless the underlying illness is prolonged.

Children who are unable to tolerate oral maintenance or stress doses during an illness require parenteral glucocorticoid administration. This is commonly initiated at home using intramuscular hydrocortisone sodium succinate at a dose of 50 mg/m² and will provide coverage for ~ 6 to 8 hours. Consultation with a health care provider is recommended. If the patient's condition does not improve or worsens, emergency evaluation and treatment with intravenous hydrocortisone should be undertaken.

Parenteral hydrocortisone is also frequently recommended before general anesthesia and surgery. A preoperative dose of 50 mg/m² 30 to 60 minutes before induction of anesthesia can be administered intravenously or intramuscularly. A second dose of 50 mg/m² can then be administered as a constant infusion or as an intravenous bolus divided every 6 hours over the next 24 hours. Intravenous or oral stress doses may be continued until the patient has recovered.

INFLUENCE OF OTHER HORMONAL DEFICIENCIES

It is well documented that initiation of thyroid hormone replacement in an individual who has hypothyroidism accompanied by unrecognized adrenal insufficiency can precipitate an adrenal crisis. The most common setting for this in the pediatric population is the patient with multiple pituitary hormone deficiencies. The mechanism that precipitates adrenal crisis is not fully understood, but it is hypothesized that hypothyroid patients have reduced cortisol requirement secondary to a reduced metabolic rate in the presence of untreated hypothyroidism.^{32,33} When thyroxine therapy is initiated, the metabolic rate and cortisol requirements increase, and an adrenal crisis is precipitated. Accordingly, hyperthyroidism can increase cortisol metabolism. It is suggested that in the individual with hyperthyroidism and adrenal insufficiency, cortisol replacement be increased as much as twofold because of increased cortisol clearance.² Pregnancy is associated with increased corticosteroid-binding globulin and free cortisol levels during the last trimester, which requires an increase in hydrocortisone by 50%.² Also, rising progesterone levels antagonize the mineralocorticoid effect, which requires adjustment of fludrocortisone supplementation as well.

GH seems to inhibit 11- β -hydroxysteroid dehydrogenase-1 activity in the liver, resulting in decreased conversion of inactive cortisone to active cortisol.³⁴ Monitoring for signs and symptoms of adrenal insufficiency is recommended for individuals with concomitant secondary adrenal insufficiency when GH therapy is initiated. Glucocorticoid therapy may need to be increased.

Dysfunction of the hypothalamic-pituitary-adrenal axis should be considered in any child diagnosed with GH deficiency, particularly those with anatomic anomalies of the pituitary or stalk on MRI, organic causes (eg, cranial surgery, tumors, trauma), and/or multiple anterior pituitary hormone deficiencies. Secondary adrenal insufficiency may evolve over time in patients with cranial radiation, septo-optic dysplasia, autoimmune hypophysitis, PROP-1 deficiency, and after head trauma.³⁵⁻³⁷ Periodic reassessment of previously normal hypothalamic-pituitary-adrenal function should be considered in patients with organic hypopituitarism.

Drugs that inhibit cortisol biosynthesis include aminoglutethimide, etomidate, ketoconazole, metyrapone, medroxyprogesterone, and megestrol.^{5,38} Drugs that accelerate cortisol metabolism are phenytoin, barbiturates, and rifampin.^{2,5,21}

"RELATIVE ADRENAL INSUFFICIENCY" IN THE ICU

Over the past decade the concept of "relative adrenal insufficiency" has been proposed in the ICU setting and generally refers to patients with vasopressor-resistant hypotension. In critically ill adults with a normal baseline cortisol level (≥ 20 $\mu\text{g}/\text{dL}$), an incremental rise of cortisol of ≤ 9 $\mu\text{g}/\text{dL}$ after 250 μg of intravenous ACTH

was associated with improved survival when treated with stress doses of hydrocortisone.³⁹

Pizarro et al⁴⁰ recently studied the baseline and peak response to 250 μg of ACTH in critically ill children with septic shock to learn if this test would predict shock resistant to vasopressors in the pediatric setting. All children (18%) with a basal serum cortisol level of < 20 $\mu\text{g}/\text{dL}$ had catecholamine-resistant shock. Eighty percent of those with a low incremental cortisol response to ACTH (≤ 9 $\mu\text{g}/\text{dL}$ at 30 or 60 minutes) compared with 20% with "normal" basal and incremental cortisol response had catecholamine-resistant shock. Adrenal insufficiency, as defined in this study, did not predict mortality. The effect of corticosteroid treatment was not specifically evaluated.

Secondary adrenal insufficiency after traumatic brain injury is another area of study in the ICU. In 80 patients (aged 14–80 years) immediately after traumatic brain injury, relative adrenal insufficiency (2 cortisol levels < 15 $\mu\text{g}/\text{dL}$ or 1 cortisol level of < 5 $\mu\text{g}/\text{dL}$) occurred in 50% of patients and was associated with lower blood pressure and increased vasopressor requirements.⁴¹ Function normalized when assessed by low-dose ACTH tests at 3 and 6 months. The benefit of providing early stress doses of glucocorticoids to patients with brain injury is currently being studied.

Measurement of circulating cortisol levels during severe illness may be problematic. Greater than 90% of circulating cortisol is protein bound. Low total cortisol but increased free basal and ACTH-stimulated cortisol levels were recently demonstrated by Hamrahian et al⁴² in 40% of critically ill patients with hypoproteinemia. Free cortisol levels were comparable to critically ill patients with normal serum protein levels and significantly higher than in healthy control subjects. Their article raised questions about the true prevalence of relative adrenal insufficiency in the ICU population. Further confirmation of circulating free cortisol levels in various physiologic states may help clarify this issue.

Controversy also exists regarding the use of physiologic stress doses of hydrocortisone in the hypotensive infant in the NICU. Sick premature infants may have relatively low cortisol responses to ACTH compared with less sick, more mature infants, which suggests an inability to mount an adequate adrenal secretory response to severe stress, possibly reflecting immaturity of the hypothalamic-pituitary-adrenal axis.^{43,44} Low cortisol levels were more prevalent in a group of premature neonates who subsequently died compared with those who survived.⁴⁵ Hydrocortisone (1 mg/kg every 8 hours) is frequently used to treat hypotension in this population, particularly those who are unresponsive to vasopressor agents. Although critically ill infants with the lowest cortisol levels respond best to hydrocortisone therapy, basal cortisol levels and cortisol and ACTH responses to CRH are variable and do not predict need for vasopres-

sors or response to hydrocortisone therapy.^{46,47} Ng et al⁴⁸ recently performed a double-blind randomized, controlled study of a stress dose of hydrocortisone (1 mg/kg every 8 hours intravenously for 5 days) versus placebo solution in 48 very low birth weight infants with hypotension requiring dopamine at ≥ 10 $\mu\text{g}/\text{kg}$ per minute. Two patients in the hydrocortisone-treated group versus 11 infants in the control group required a second vasopressor, which suggested benefit. Although hydrocortisone in this population seems to be an important tool in achieving cardiovascular stability, its long-term safety in this population has not been established. During a large randomized multicenter trial of hydrocortisone treatment in very low birth weight infants, an increase of spontaneous gastrointestinal perforations was found in the treated infants, particularly with concomitant use of indomethacin.⁴⁹ Hydrocortisone may enhance the vasoconstrictive effects of dopamine or epinephrine, possibly reducing tissue perfusion. Long-term effects of hydrocortisone on neurodevelopmental outcome are unknown.

Whether the critically ill very premature infant has relative or absolute adrenal insufficiency is still not certain; however, hydrocortisone can usually be weaned if the infant remains stable; endogenous glucocorticoid secretion seems to normalize as the infant matures.⁴⁶

As in older children and adults, normative data are needed regarding basal and stimulated free serum cortisol levels in premature and term neonates.

WAYS TO IMPROVE EDUCATION REGARDING STRESS DOSING IN PATIENTS WITH KNOWN ADRENAL INSUFFICIENCY

Morbidity and mortality associated with adrenal insufficiency remain unnecessarily high. The following measures are suggested when caring for these children:

1. Provide written instructions to the patient and family regarding how and when to increase glucocorticoid therapy; review the instructions at each visit or at least yearly so that the dose can be appropriately increased as the child grows.
2. Instruct the family on the use of intramuscular hydrocortisone sodium succinate in case of vomiting illness or severe stress; review the dosage yearly so that it is increased with growth of the child.
3. Advise the use of a medical alert bracelet or necklace stating the diagnosis of adrenal insufficiency and the need to administer hydrocortisone.
4. In young children prone to hypoglycemia, having home blood glucose monitoring equipment and glucose gel in the home may be indicated.
5. Sugar-containing snacks should be provided with prolonged or strenuous exercise because of epinephrine deficiency in children with adrenal insufficiency.

6. Advise patients and their caretakers to seek medical consultation if the patient becomes ill.
7. Consider preparing a letter to be mailed to the family's local emergency medical services to notify them of the patient's diagnosis and place of residence so that, if they are called to the home, hydrocortisone can be administered without delay. This may be particularly important if not all family members are willing or able to administer the intramuscular injection independently.
8. Continuing education is needed for primary care physicians and emergency department physicians regarding signs and symptoms and appropriate treatment of adrenal insufficiency.
9. Some children and adolescents with adrenal insufficiency will never be capable of recognizing and treating an adrenal crisis. Safeguards should be in place to ensure oversight as these children become more independent.
10. Individuals who have been on long-term (>2 weeks) pharmacologic doses of glucocorticoids should be considered at risk for adrenal insufficiency.
11. Patients who require long-term exogenous glucocorticoid therapy should be weaned to doses that are less than physiologic or given every other day to help avoid the risk of adrenal insufficiency.

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