Abstract:
Adrenal insufficiency is an important and potentially life-threatening condition that may present to the emergency department. Seven clinical scenarios of adrenal insufficiency that the emergency physician should be able to recognize and confidently manage are reviewed. Epidemiology and mortality, etiology, and pathophysiology are addressed. Clinical presentation, diagnosis, and management of acute and chronic adrenal disease are also covered. In particular, adrenal suppression due to exogenous steroid use, adrenal suppression in septic shock, and adrenal suppression associated with etomidate are reviewed.

Keywords:
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Adrenal Insufficiency in the Pediatric Emergency Department

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CASE 1

A 12-year-old girl with congenital adrenal hyperplasia (CAH) who is on maintenance doses of a glucocorticoid and mineralocorticoid presents to the emergency department (ED) with a 3-day history of cough, congestion, and sore throat. Today, the patient also complains of fatigue. At triage, her vital signs are as follows: temperature (T) 39.0°C; heart rate (HR) 110 beats/min; respiratory rate (RR) 20 breaths/min; and blood pressure (BP) 110/60 mm Hg. On examination, she appears tired but does not have any focal findings. Her blood glucose is 80 mg/dL. Her mother informs the ED staff that the patient needs extra steroids. The ED physician caring for her is hesitant to do this because the patient appears to be relatively well. After a discussion with the patient's endocrinologist, the patient's hydrocortisone dose is tripled (increasing the dose per meter squared from 9 to 27 mg/m^2).

Mortality Due to Adrenal Insufficiency

This patient does not appear critically ill on examination, but she is actually at high risk for developing an adrenal crisis due her underlying adrenal insufficiency. Cohort studies demonstrate higher risk of morbidity and mortality in adrenal insufficiency. Increased mortality in adrenal insufficiency is not only due to delayed treatment of the undiagnosed patient, but it is also due to

adrenal crisis in a patient with known adrenal insufficiency who fails to receive adequate glucocorticoid supplementation in conditions of increased metabolic demand.[1,2]

A review of patients with CAH treated in Europe from 1969 to 1998 found a 5-fold increased risk of mortality within the first year of life (11.9% compared with 2.9%).[3] Similarly, a retrospective review of patients with CAH treated in the United Kingdom from 1964 to 1996 found a 3-fold increased risk of mortality at all ages and an 18-fold increased risk at ages 1 to 4 years; 1.8% of patients died during a concurrent infection.[4] A retrospective review of Finnish patients with CAH treated from 1980 to 1995 found 4.6% mortality connected to glucocorticoid deficiency. The Finnish study also noted that 9.3% of patients were admitted to the hospital at least once for severe illness related to cortisol insufficiency.[5]

A Swedish population-based study of mortality in Addison's disease found that the risk ratio for death was twice as high for patients with primary adrenal insufficiency compared with baseline population mortality rates. This study, which examined both pediatric and adult patients with Addison disease, found that the primary etiologies for death were infections, cardiovascular, and malignancy.[6] The authors speculated that increased mortality during illness was due to inadequate steroid supplementation in the context of increased physiologic stress.[6] A similar Norwegian study of patients with Addison disease found that patients diagnosed before age 40 years had a 1.5- to 2-fold increase in their mortality rate. Specifically, mortality rates due to infection and sudden death were greater for patients with Addison disease compared with the baseline population, and the authors reported that many patients died in the context of "trivial infections".[7]

In addition, patients with adrenal insufficiency due to abnormalities of the hypothalamic-pituitary axis seem to be at increased risk for mortality.[1,8-10] A Canadian cohort study of patients treated with growth hormone (GH) from 1967 to 1992 found that 24% of the total deaths in this cohort were due to adrenal crisis or hypoglycemia.[8] A similar cohort study from the United Kingdom examining patients treated with GH from 1972 to 1990 found that 19% of deaths were either due to hypopituitarism or acute infection.[9] Finally, a cohort of GH-treated patients in the United States who were followed from 1963 to 1985 found that the relative risk of mortality compared with the general population was 3-fold; the subgroup in this cohort that had adrenal insufficiency experienced a relative risk of death of 7.1. Twenty-five percent of deaths in this cohort were sudden and unexpected, and the authors suspected adrenal insufficiency as the cause in at least 50% of these cases.[10]

Etiology and Pathophysiology of Adrenal Insufficiency

Adrenal insufficiency may be categorized into 2 separate entities, primary and secondary. In primary adrenal insufficiency, the adrenal gland is the site of dysfunction, either due to a developmental abnormality such as an enzyme defect, or due to tissue destruction. In primary adrenal disease, glucocorticoid production is blocked, and mineralocorticoid production may also be absent.

Secondary adrenal insufficiency may be defined as a defect in the hypothalamic-pituitary-adrenal (HPA) axis that results in low or no adrenocorticotrophic hormone (ACTH) production. Secondary adrenal insufficiency most commonly arises from hypothalamic suppression due to exogenous glucorticoid administration. It may also arise from a hypothalamic or pituitary abnormality that decreases or eliminates ACTH production. In secondary adrenal insufficiency, a lack of ACTH stimulation causes atrophy of the adrenal cortex in the zona fasciculata and zona reticularis. The atrophied adrenal gland will then exhibit decreased responsiveness if re-exposed to ACTH. This is the reason for acute adrenal insufficiency when chronic steroids are abruptly discontinued. In secondary adrenal insufficiency, although glucocorticoid production is deficient, mineralocorticoid production is preserved. This occurs because the zona glomerulosa, the adrenal cortical region that produces mineralocorticoid, is activated by the renin-angiotensin system, not by ACTH.[11]

In both primary and secondary adrenal insufficiency, the production of adrenal steroids may be completely interrupted or relatively suppressed. When adrenal insufficiency is relative, there will be a reduced or insufficient response in the setting of increased metabolic demand.[1,11]

Primary Adrenal Insufficiency

The prevalence of primary adrenal insufficiency in adults is 93 to 140 per million.[1,12-16] In developed nations, autoimmune adrenalitis is the most common cause of primary adrenal insufficiency in adults.[12] Tuberculous adrenal disease remains a very common etiology in the developing world.[1,17] Adrenal insufficiency is much less common in children than it is in adults. The most common etiology of primary adrenal insufficiency in

childhood is CAH, occurring in 1 of every 10-18 000 children.[18] Other common pediatric etiologies are autoimmune adrenal failure, adrenoleukodystrophy, congenital adrenal hypoplasia, hemorrhage due to birth trauma associated with asphyxia, other trauma, meningococcemia, and other infections. A more extensive list is provided in Table 1.[1]

In a 20-year review of 103 children treated for primary adrenal insufficiency in Montreal, 71.8% of cases were due to CAH. Of the remaining 28%, 13 (12.6%) patients had autoimmune adrenal insufficiency, 4 had adrenoleukodystrophy, and 3 had Wolman disease. One patient had Allgrove syndrome, 1 had Zellweger disease, and 1 had X-linked congenital adrenal hypoplasia. Two patients had unexplained glucocorticoid deficiency, and 2 patients had unexplained glucocorticoid and mineralocorticoid deficiencies.[19] A 20-year retrospective study of patients treated for adrenal insufficiency in Thailand had similar results. In this study, there were 62 children with primary adrenal insufficiency. Eighty-seven percent of these patients had CAH. Five percent of patients had ACTH unresponsiveness, 2 children had familial glucocorticoid deficiency, and 1 had Allgrove syndrome. Five patients (8%) had no diagnosed cause.[20] A 10-year retrospective study of non-CAH primary adrenal insufficiency in Australian children identified 16 cases. Five patients each were diagnosed with Addison disease and adrenoleukodystrophy. Six patients were diagnosed with congenital adrenal hypoplasia.[21]

TABLE 1. Etiology of primary adrenal insufficiency.

Congenital
Congential adrenal hyperplasia
Congenital adrenal hypoplasia
Familial glucocorticoid deficiency (ACTH unresponsiveness)
Allgrove syndrome (alachrima, achalasia, ACTH unresponsiveness)
Metabolic disease
Adrenoleukodystrophy
Smith-Lemli-Opitz syndrome
Wolman disease
Zellweger disease
Mitochondrial disease
Acquired
Autoimmune adrenalitis (Addison disease)
Isolated autoimmune adrenalitis
Autoimmune polyendocrine syndrome
Hemorrhage
Birth trauma
Trauma
Meningococcemia (Waterhouse-Friderichsen syndrome)
Medication
Ketoconazole
Etomidate
Infection
Cytomegalovirus
Human immunodeficiency virus
Fungal
Tuberculosis

Secondary Adrenal Insufficiency

Secondary adrenal insufficiency has a much greater prevalence, with 150 to 280 cases per million.[12,15,22-25] The most common cause of secondary adrenal insufficiency is iatrogenic HPA axis suppression due to glucocorticoid administration.[12] Secondary adrenal insufficiency can also arise from congenital or acquired defects of the hypothalamus or pituitary gland (Table 2).[1] It is extremely important to note that secondary adrenal insufficiency may develop months to years after cranial irradiation or traumatic brain injury, and delayed onset may also be the case with some congenital malformations, particularly septo-optic dysplasia.[1,26-28]

Previously, unexpected sudden death in patients with Prader-Willi syndrome had been attributed only to sleep apnea. Recently, the additional possibility of HPA axis abnormalities was considered in light of the known abnormality in the GH axis of these patients and in light of the increased incidence of sudden death in patients with HPA axis deficiency. These suspicions were confirmed by a recent study of hypothalamic-pituitary function in patients with Prader-Willi syndrome. In this investigation, 25 children with Prader-Willi syndrome underwent an overnight metyrapone test, and 15 (60%) had an insufficient ACTH response.[29]

CASE 2

A 10-day-old full-term male infant born to a 23-year-old gravida 1, para 1 mother is brought to the ED with a chief complaint of "spitting up." Pregnancy was complicated by the absence of prenatal care. The patient has not been seen by his pediatrician since hospital discharge. His mother reports that he has become progressively sleepier since 4 days of age and that he has experienced increased frequency of spitting up. The patient has taken 1 to 2 oz of premixed formula 3 times today and has had 2 slightly wet diapers. On physical examination, the infant is very ill appearing with the following vital signs: T 37°C; HR 190 beats/min; RR 45 breaths/min; and BP 50/30 mm Hg. His

TABLE 2. Etiology of secondary adrenal insufficiency.

Congenital
Septo-optic dysplasia
Maternal hypercortisolemia (hypothalamic suppression)
Corticotropin releasing hormone deficiency (hypothalamic dysfunction)
ACTH deficiency (pituitary dysfunction)
Pituitary aplasia/hypoplasia
Prader-Willi syndrome
Acquired
Chronic steroid use
Abrupt steroid withdrawal
Increased metabolic demand
Megesterol acetate (Megace) withdrawal
Tumor
Head trauma
Burn injury
Radiation
Infiltrative disease

fontanelle is sunken, the oropharynx is sticky, and the extremities are cool with a capillary refill time greater than 3 seconds. Accu-chek blood glucose is 40 mg/dL. Vascular access is obtained and a 10% dextrose bolus is given producing a rise in blood glucose to 80 mg/dL, and 2 normal saline boluses are given with a slight improvement in the infant's perfusion. A workup for sepsis is performed, and the patient is given antibiotics. The laboratory evaluation reveals that the serum sodium is 125 mEq/L, potassium is 6.7 mEq/L, chloride is 99 mEq/L, bicarbonate is 17 mEq/L, blood urea nitrogen (BUN) is 15 mg/dL, and creatinine is 0.6 mg/dL. Acute adrenal insufficiency is suspected. A stress dose of hydrocortisone (50 mg/m^2) is administered after drawing blood for measurement of cortisol, ACTH, dehydroepiandrosterone, 17-hydroxyprogesterone, aldosterone, and renin.

Clinical Presentation of Acute Adrenal Insufficiency

This patient is presenting with acute adrenal insufficiency, most likely due to undiagnosed CAH. Acute adrenal insufficiency, synonymous with adrenal crisis, is a severe life-threatening condition due to cortisol ± mineralocorticoid deficiency. Acute adrenal insufficiency may present with dehydration, hypotension, nausea, vomiting, weakness, abdominal pain, and sometimes fever. A patient with unrecognized acute adrenal insufficiency will progress to shock and ultimately cardiovascular collapse. On occasion, patients may be misdiagnosed with a surgical abdomen. Altered mental status or coma may also be present. Infants and toddlers may present with hypoglycemia and seizures.[1,12] An adrenal crisis may be precipitated by increased metabolic demands such as illness, trauma, surgery, or excess heat but may also occur without an evident trigger.[1,30] Because the initial signs of adrenal insufficiency are subtle, patients often are not diagnosed until a true adrenal crisis has developed.[21,31] In the most severe forms of adrenal insufficiency, such as the "salt wasting" form of CAH, both glucocorticoid and mineralocorticoid production are absent. Because both glucocorticoids (cortisol) and mineralocorticoids (aldosterone) maintain normotension, patients with deficiencies of both have profound dehydration and hypotension.

Cortisol works to maintain BP through a variety of mechanisms. It is responsible for conversion of norepinephrine to epinephrine in the adrenal medulla. Cortisol also improves capillary integrity and contributes to vasoconstriction by inhibiting arterial wall nitric oxide synthesis. Cortisol also has inotropic effects and improves cardiac output. In addition, glucocorticoids potentiate the vascular and cardiac action of epinephrine and norepinephrine. In conditions of increased metabolic demand (in which cortisol production increases markedly), cortisol also acts like a mineralocorticoid by promoting sodium and water retention. Mineralocorticoids contribute to normotension and normovolemia by promoting sodium and water reabsorption in the distal tubules and collecting ducts of the kidney.[1,32,33]

CAH and Acute Adrenal Insufficiency

The prior scenario is typical for an infant with CAH presenting in adrenal crisis. Congenital adrenal hyperplasia, which is due to one of several possible defects in the enzymatic pathway of cortisol synthesis, results in an overproduction of ACTH and hyperplasia of the adrenal cortex. Depending on the enzymatic defect, cortisol insufficiency is partial or complete. Also, aldosterone deficiency may or may not be present. The most common enzymatic deficiency, 21-hydroxylase deficiency, accounts for 90% of cases.[18]

In 21-hydroxylase deficiency, overproduction of ACTH drives excessive testosterone production, causing virilized or ambiguous genitalia in affected female infants. As a result of ambiguous or virilized genitalia, female infants have historically been

diagnosed at birth, but before newborn screening, male infants did not usually present until adrenal crisis had supervened. In a review of primary adrenal insufficiency in Montreal, male infants with CAH presented significantly later than did female infants, and 20 of 26 (77%) male infants with the salt wasting form of CAH presented with adrenal crisis, with 3 of these patients presenting in cardiac arrest.[19] Retrospective reviews of patients with CAH treated in Europe and Finland found that the time to diagnosis was also significantly longer for male than female patients.[3,5] As a result of missed and/or delayed diagnoses of 21-hydroxylase deficiency, many industrialized countries have implemented mandatory newborn screening programs. Currently, all state newborn screening programs in the United States evaluate for CAH due to 21-hydroxylase deficiency. Without such screening, experts estimate that there would be a 4% to 9% mortality rate due to undiagnosed CAH in industrialized countries.[34-36]

CASE 3

A 12-year-old girl with no significant previous illnesses presents to the ED with a chief complaint of fatigue, nausea, and vomiting. She initially began complaining of fatigue 3 months previously. She has seen her pediatrician several times over this time. Tests for mononucleosis and thyroid dysfunction were negative. She was subsequently diagnosed with depression, for which she is seeing a therapist. She has not attended school for the past 2 weeks because of the fatigue. Nausea, abdominal pain, and vomiting have developed during the past 2 days. She is having 3 to 5 episodes of nonbilious, nonbloody emesis per day. On physical examination, she is a thin, listless girl who appears quite tanned. Her vital signs are as follows: T 37.3°C; HR 130 beats/min; RR 20 breaths/min; and BP 110/60 mm Hg. Her weight is 40 kg and her oxygen saturation in room air is 99%. The patient has dry mucous membranes and a 3-second capillary refill time. She has prominently tanned skin, including hyperpigmentation of the axillae, palmar creases, and mucous membranes. The rest of her physical examination is within normal limits. Laboratory evaluation reveals a serum sodium of 123 mEq/L, potassium of 4 mEq/L, chloride of 99 mEq/L, bicarbonate of 18 mEq/l, BUN of 20 mg/dL, creatinine of 0.6 mg/dL and glucose of 80 mg/dL.

Adrenal insufficiency is suspected in this 12-year-old, and several intravenous (IV) fluid boluses are administered. Blood is also drawn for cortisol, ACTH, aldosterone, and renin levels. Then a presumptive bolus of hydrocortisone is given at a dose of 50 mg/m^2. The cortisol level later returns at 10 mg/dL, and the ACTH level is 120 pg/dL. Endocrinology is consulted and they agree to admit the patient for continued fluid and electrolyte replacement and further steroid management.

Clinical Presentation of Chronic Adrenal Insufficiency

The patient in this scenario has Addison disease (autoimmune adrenal failure) and is presenting in chronic adrenal failure. Chronic adrenal insufficiency initially manifests with subtle, nonspecific symptoms. Symptoms are frequently attributed to a primary gastrointestinal or psychiatric problem, and diagnosis is often delayed, sometimes by several years.[1,12,14,21] Chronic adrenal insufficiency may manifest with fatigue, irritability, weakness, weight loss, and anorexia. Patients frequently manifest a change in mood or behavior; most commonly, apathy, depression, or irritability is present.[37] In chronic primary adrenal insufficiency, patients may report salt craving or dizziness, and postural hypotension may be present on examination. Chronic nausea, vomiting, and abdominal pain may also be present; this is thought to be a consequence of decreased gut motility.[38] Skin hyperpigmentation, which is a consequence of increased melanocyte activity as a result of overproduction of melanocyte-stimulating hormone, which is contained within ACTH and ACTH precursors, is found only in primary adrenal insufficiency. Skin changes may be subtle and are most apparent in the axillae, palmar creases, knuckles, and oral mucosa. Conversely, in secondary adrenal insufficiency, patients may exhibit extreme pallor due to decreased ACTH production and thus decreased melanocyte stimulation.[12]

Additional pertinent history includes a medical history or a family history of endocrine or autoimmune disease. In particular, patients with signs of pituitary insufficiency (growth or pubertal delay) or known pituitary disease would raise suspicion for undiagnosed secondary adrenal insufficiency.[1] Chronic adrenal insufficiency due to an autoimmune polyendocrine syndrome may manifest alongside symptoms of other endocrine or autoimmune disorders. Most notably, chronic mucocutaneous candidiasis is present along with adrenal insufficiency in autoimmune polyendocrine syndrome type 1, and hypothyroidism, diabetes mellitus, vitiligo, or alopecia may be present in autoimmune polyendocrine syndrome type 2.[12,39,40]

Laboratory Findings in Adrenal Insufficiency

Cortisol deficiency may lead to hypoglycemia and may cause mild anemia, lymphocytosis, and eosinophilia. Occasionally, hypercalcemia is present.[12,41] If mineralocorticoid deficiency is present, aldosterone will be low and renin will be elevated; usually hyponatremia, hyperkalemia, and acidosis develop.[1] However, electrolyte imbalances are not requisite. In a large series of patients with Addison disease, 88% of patients presented with hyponatremia, 64% of patients with hyperkalemia, and 6% with hypercalcemia.[41,42]

In secondary adrenal insufficiency, although aldosterone is present, hyponatremia may occur because cortisol is not present to inhibit vasopressin release. In the absence of the inhibitory effect of glucocorticoids, excess antidiuretic hormone is released, leading to total body water overload and hyponatremia. Hyperkalemia is not present in this setting, and this may assist in differentiating hyponatremia due to glucocorticoid deficiency from hyponatremia due to aldosterone deficiency.[43]

Confirmatory Diagnostic Testing: Primary Adrenal Insufficiency

Primary adrenal insufficiency is detected by elevated ACTH and low cortisol levels. Adrenocorticotrophic hormone levels are often greater than 100 pg/mL, and cortisol levels are usually less than 10 μg/dL.[1] However, a normal serum or urine cortisol level may be under the detection threshold for many laboratory assays, so a low cortisol level alone may not be diagnostic.[44] In addition, serum cortisol measurements may not accurately reflect bioavailable free cortisol because most cortisol is protein bound and inactive. In hypoproteinemia, a low cortisol level may not accurately reflect available free cortisol.[1] A diagnosis of primary adrenal insufficiency may be made if basal levels of cortisol are meager in the face of elevated levels of ACTH. The most definitive diagnostic test is cortisol response to an ACTH stimulation test; this test will typically reveal an inadequate cortisol response (less than 18 μg/dL).[1,44] In CAH due to 21-hydroxylase deficiency, diagnosis is confirmed with markedly elevated 17-hydroxyprogesterone levels but subnormal cortisol levels in response to the ACTH stimulation test.[45] If mineralocorticoid deficiency is present, aldosterone levels will be low and renin levels will be elevated.[1]

CASE 4

A 9-year-old with a medical history of medulloblastoma that was successfully treated with craniospinal irradiation and high-dose chemotherapy presents to the ED with a several week history of fatigue and nausea. He is taking GH replacement. On examination, the child appears listless and 5% to 10% dehydrated. His vital signs are as follows: T 37.1°C; HR 130 beats/min; RR 20 breaths/min; and BP 100/60 mm Hg. A serum electrolyte panel reveals a sodium of 125 mEq/L, potassium of 4 mEq/L, chloride of 99 mEq/L, bicarbonate of 17 mEq/L, and glucose of 50 mg/dL. Two normal saline boluses and a 10% dextrose bolus are administered without significant improvement in the patient's HR or BP. Secondary adrenal insufficiency is suspected because of his previous craniospinal irradiation and known GH insufficiency. Serum cortisol, ACTH, GH, and insulin levels are obtained, and hydrocortisone is administered. The serum cortisol returns at 5 μg/dL. The on-call endocrinologist agrees to admit the patient for IV rehydration, further steroid therapy, and repeat laboratory workup.

Confirmatory Diagnostic Testing: Secondary Adrenal Insufficiency

In secondary adrenal insufficiency, ACTH and cortisol levels are both low. An 8 AM cortisol level less than 3 μg/dL supports the diagnosis, and a level greater than or equal to 10 μg/dL suggests normal adrenal function. The diagnosis can be confirmed by a variety of tests. The insulin tolerance test, considered the criterion standard, carries the risks of hypoglycemic seizure or hypokalemia.[1,46] Other studies that may confirm secondary adrenal insufficiency include both low- and regular-dose ACTH stimulation tests, the corticotrophin-releasing hormone stimulation test, the glucagon stimulation test, and overnight metyrapone testing.

None of the supplemental diagnostic tests for secondary adrenal insufficiency are completely reliable. False-positive rates for the low-dose ACTH stimulation test in 2 studies of infants and children ranged from 21% to 29%.[47-50] In addition, the central adrenal insufficiency may still be early enough in development that the adrenal cortex will exhibit some response to ACTH stimulation.[47]

CASE 5

A 17-year-old boy presents to the ED with a 3-day history of nausea, vomiting, and progressive fatigue and now appears disoriented. He was recently diagnosed with hypothyroidism and began taking synthroid 1 week ago. There is also a strong family history for thyroid disease. On arrival to the ED, his vital signs are as follows: T 37°C; HR 130 beats/min;

RR 25 breaths/min; and BP 90/50 mm Hg. On examination, he appears disoriented and lethargic. His mucous membranes are dry, but hyperpigmented patches are noted on his tongue and gray lines are seen on his gums. His abdomen is soft but diffusely tender. His extremities are cool with a 3-second capillary refill time. An accucheck blood glucose is 50 mg/dL. A serum electrolyte panel reveals a sodium of 123 mEq/L, potassium of 5.5 mEq/L, chloride of 98 mEq/L, bicarbonate of 16 mEq/L, BUN of 15 mg/dL, and creatinine of 0.8 mg/dL. As an adrenal crisis is suspected, blood is drawn for assays of cortisol, ACTH, renin, and aldosterone. Two boluses of 10% dextrose in normal saline and hydrocortisone (50 mg/m^2) are administered.

Management of Acute Adrenal Insufficiency

Initiation of thyroid hormone replacement in patients with undiagnosed primary or secondary adrenal insufficiency is known to precipitate an adrenal crisis. The mechanism is speculated to be due to an increase in cortisol catabolism triggered by increasing levels of thyroid hormones.[1,51,52] Growth hormone initiation may also precipitate adrenal crisis in undiagnosed adrenal insufficiency.[53]

The management of acute adrenal insufficiency includes rapid volume resuscitation with isotonic fluids, correction of hypoglycemia, and administration of stress doses of steroids. Hydrocortisone, which in high doses exhibits both glucocorticoid and mineralocorticoid activity, is the treatment of choice. The first dose of hydrocortisone should be administered as an IV bolus (50-100 mg/m^2).[1,54] Equivalent stress glucocorticoid activity can be achieved with methylprednisolone (10-15 mg/m^2) or dexamethasone (1.5-2 mg/m^2). Neither methylprednisolone nor dexamethasone has sufficient mineralocorticoid activity, so they are not used when mineralocorticoid replacement is needed. Prednisone should not be used because it must undergo metabolism in the liver before achieving a glucocorticoid effect.[1] If IV access cannot be obtained, intramuscular hydrocortisone can be given, but absorption by the intramuscular route is slower than it is by the IV route and may therefore be insufficient if the patient is profoundly dehydrated.[1] After this, hydrocortisone (12-25 mg/m^2 IV every 6 hours) may be administered.[30,54] Body surface area may be calculated from the body surface area nomogram by Briars or Mosteller's formula[54-56]:

$$\text{BSA}\left(\text{m}^2\right) = \text{square root of}\{[\text{height(cm)} \times \text{weight(kg)}]/3600\}.$$

Clinical improvement should be exhibited within 4 to 6 hours of glucocorticoid administration.[32]

If rapid volume resuscitation is contraindicated due to cardiac or renal disease, electrolyte balance in the mineralocorticoid deficient patient may also be achieved by initiating oral fludrocortisone (0.1-0.2 mg/d). Fludrocortisone has 400 times the mineralocorticoid potency of hydrocortisone.[1,12]

Maintenance Dosing

Once the patient has been stabilized, they can be transitioned to a maintenance dose of a glucocorticoid, mineralocorticoid, and sodium supplementation. In patients with primary adrenal insufficiency, cortisol is typically supplemented with hydrocortisone (7-10 mg/m^2 per day).[1] Because secondary adrenal insufficiency is sometimes partial, patients with secondary adrenal insufficiency may need a smaller amount of glucocorticoid replacement.[1] Supplementation should be modified based on the patient's symptoms and not based on the ACTH level because this alone is an inaccurate measure of sufficient replacement.[1]

The typical maintenance mineralocorticoid replacement for patients who are aldosterone insufficient is oral fludrocortisone (0.1-0.2 mg/day).[1] Infants with mineralocorticoid deficiency will also require 1 to 2 g of sodium chloride supplementation per day. Potassium levels give an estimate of sufficient supplementation; oversupplementation may lead to edema, hypertension, headache, and hypokalemia.[5]

Stress Dosing

Returning to the first clinical scenario with the 12-year-old with CAH, fever, and fatigue, stress dose steroids should be given. If patients do not receive adequate boosts in glucocorticoid replacement for increased metabolic need, they are at high risk for significant morbidity and mortality due to adrenal crisis.

The aim of extra glucocorticoid replacement is to match what the body would have produced with an intact HPA axis. The threshold for what constitutes a metabolic "stress" that warrants increased steroid administration is debatable, and consultation with the patient's endocrinologist is recommended. Generally, acute illness and trauma require supplementation. Expert guidelines for stress dosing recommend doubling to tripling the daily dose of glucocorticoid. Other recommendations suggest increasing hydrocortisone to 30 to 50 mg/m^2 divided into 3 to 4 doses per day. Illnesses that particularly necessitate stress dose steroids are those with fever, vomiting, diarrhea, poor oral intake, or fatigue. The standard preoperative stress dose of hydrocortisone is 50 to 100 mg/m^2 with subsequent doses

administered over 24 to 48 hours, usually at 6-hour intervals. Sepsis and major surgery require greater replacement, with some recommending 25 mg/m^2 every 6 hours.[1,44,54]

CASE 6

A 5-year-old girl with moderate persistent asthma presents to the ED with a complaint of fever, fatigue, and 2 days of abdominal pain. Three days ago, she finished a 5-day course of prednisone (2 mg/kg/day). Her vital signs on arrival are as follows: T 37°C; HR 120 beats/min; RR 30 breaths/min; and BP 80/40 mm Hg. On examination, she appears fatigued and mildly dehydrated. She has right lower quadrant tenderness on palpation of her abdomen with rebound and guarding. Appendicitis is suspected and surgery is notified. As she is being prepped for surgery, the anesthesiologist asks what is the likelihood that this patient has adrenal suppression as a consequence of her recent course of steroids.

HPA Suppression Due to Exogenous Glucocorticoids

This patient may be at increased risk for adrenal suppression as a consequence of her recent course of high-dose steroids. The likelihood for adrenal suppression is dependent on steroid dose, duration of the course, and how recently the course of steroids was completed.[57] Experts agree that greater than 2 weeks of glucocorticoid therapy will place a patient at high risk for adrenal insufficiency.[1] Conversely, steroid courses under 2 weeks and doses less than physiologic glucocorticoid replacement do not usually cause "clinically important" adrenal suppression.[57] A study measuring HPA response via an insulin hypoglycemic test in children with asthma after a 5-day course of steroids showed a high incidence of adrenal suppression 3 days after burst completion. Adrenal response had normalized by 10 days after the short course of steroids.[58] Conversely, adrenal function in children with asthma who received frequent courses of oral steroids but who had not received a course within the past month found no adrenal suppression in response to ACTH stimulation testing.[59]

In patients who receive a prolonged course of glucocorticoids followed by a steroid taper, adrenal suppression is still often present for a prolonged period after the taper. In a study of 64 pediatric patients with leukemia undergoing induction chemotherapy that included a 4-week course of high-dose prednisone or dexamethasone and a 9-day taper, 63% exhibited a low morning cortisol, and 82% had an insufficient response to ACTH stimulation testing on the day after steroid discontinuation. At 1 to 2 weeks after steroid discontinuation, 23% still exhibited inadequate responses to ACTH stimulation testing. Responses normalized in all patients by 10 weeks.[60] A smaller study of adrenal function in 15 patients with leukemia undergoing induction chemotherapy with high-dose dexamethasone found an abnormal cortisol response to the corticotrophin-releasing hormone test in 40% of patients at 2 weeks after discontinuation of dexamethasone.[61]

A study of adrenal function was performed in 13 infants who had recently completed a prolonged course of oral steroids for hemangioma reduction. The patients had received 1 month of high-dose steroids, with prolonged tapering over a mean of 7 months. Low- and high-dose ACTH stimulation testing was performed in all infants at an average of 13 days after completing steroid therapy, and only 1 infant had an abnormally low cortisol response. Testing had been performed on the day after completion of steroid administration. At 3 months, adrenal function had returned to normal for this patient.[62]

Adrenal insufficiency has been also reported in children receiving high doses of inhaled fluticasone (> 400 μg/d).[63,64] A cohort of 217 children receiving 500 μg/d or more of inhaled fluticasone underwent low-dose ACTH stimulation tests. Overall, 2.8% exhibited an insufficient adrenal response, and 40% exhibited a reduced adrenal response; this study did not report on concurrent or recent oral steroid use for this cohort. However, a recent state of the art review of adrenal axis testing for patients receiving inhaled corticosteroids determined that the evidence was not sufficient to support an association between inhaled steroids and adrenal suppression.[65]

CASE 7

A 6-year-old girl presents with a 3-day history of fever, sore throat, and congestion. She was initially seen by her primary care physician who diagnosed her with a viral illness. Her parents bring her to the ED because the patient has been drinking poorly and has seemed "too sleepy" over the past several hours. At ED triage, her vital signs are as follows: T 40°C; HR 160 beats/min; RR 40 breaths/min; and BP 75/40 mm Hg, and her oxygen saturation is 96% in room air. On physical examination, the child appears pale and lethargic and is difficult to arouse, though there is no meningismus. Sinus tachycardia is appreciated without murmur, rub, or gallop. Her breath sounds are clear bilaterally, and she has mild

intercostal and subcostal retractions. The abdomen is soft, and her extremities are cool with a 4-second capillary refill time.

The patient is placed on 100% oxygen via face mask with improvement in her work of breathing, and her oxygen saturation rises to 100%. Intravenous access and blood cultures are obtained. Broad-spectrum antibiotics are administered, whereas three 20 mL/kg boluses of normal saline are given without significant improvement in her HR or BP. An infusion of dopamine is begun followed by an infusion of epinephrine. The patient remains hypotensive even with maximum dose epinephrine at 10 μg/kg/min.

Adrenal Insufficiency in Acute Illness, Septic Shock

Experts have begun to recognize that a subset of patients with acute stressors such as septic shock, traumatic brain injury, or burns have an inadequate glucocorticoid response relative to the stress at hand.[1,2,66-68] This inadequate response in the setting of extreme metabolic stress is known as "relative adrenal insufficiency".[1,2,66] A variety of mechanisms have been proposed. These include cytokine, vasoactive agent and neuropeptide inhibition of ACTH receptors, modification of adrenal performance, and promotion of glucocorticoid resistance.[2,69]

No consensus definitions exist for the diagnosis of adrenal insufficiency in critical illness.[2,66,70,71] Many experts consider that adrenal insufficiency is present if, in response to a low-dose ACTH stimulation test, cortisol levels remain 25 μg/dL or less or if there is a rise of less than 9 μg/dL from baseline.[2] Other experts consider that a baseline cortisol level less than 18 μg/dL and an absolute rise of cortisol level less than 18 μg/dL to be the most predictive for relative adrenal insufficiency.[72,73] There is a high incidence of relative adrenal insufficiency in pediatric critical illness. In a prospective evaluation of endocrine function in 73 critically ill pediatric patients, 58% had baseline cortisol levels less than 25 μg/dL, and 32% had cortisol levels less than 15 μg/dL. In this study, proportions with adrenal insufficiency were similar in children with septic shock and other critical illness.[70] The degree of relative adrenal insufficiency seems to be related to patient outcome. Multiple studies of pediatric septic shock have found that plasma cortisol levels are higher in survivors compared with nonsurvivors.[66,73]

The evidence is lacking, however, for whether critically ill pediatric patients with relative adrenal insufficiency benefit from stress dose steroid administration.[66,73] Studies investigating steroid therapy for dengue shock in children have led to conflicting results,[74-77] and a study of low-dose dexamethasone given every 8 hours to African children with septic shock did not improve their survival.[78] A large retrospective study of the pediatric health information database examined variables associated with outcome in severe sepsis for 6693 patients. In this study, the mortality rate for children who did not receive steroids was 18% compared with 30% for those who did receive steroids.[79]

Based on the available data, the American College of Critical Care Medicine recommends only initiating stress dose steroids in septic shock for those pediatric patients who are catecholamine resistant and for those with risk for (or known) adrenal insufficiency and HPA suppression or for those children in whom there is clinical evidence to suggest adrenal insufficiency, such as purpura fulminans. The recommended stress dose for hydrocortisone in this setting is a range of 2 to 50 mg/kg/day in either continuous or divided doses.[72] These recommendations remain controversial, and an alternative approach has been suggested. The alternative proposal is to initiate hydrocortisone for all pediatric patients with catecholamine resistant shock. The recommended dose of hydrocortisone for the alternative guideline is a bolus of 50 mg/kg, followed by a 24-hour infusion of 50 mg/kg. A proposed definition for catecholamine resistant shock is no improvement after 1 hour of norepinephrine infusion (0.2 μg/kg/min).[80]

Controversy also surrounds the use of etomidate for intubation in septic shock because it directly halts synthesis of cortisol by inhibition of 11-β-hydroxylase.[81] A prospective adult study of patients with critical illness who were intubated with etomidate found a high incidence (80%) of adrenal suppression in response to the ACTH stimulation test.[82] Two retrospective adult studies of patients with septic shock found a greater incidence of adrenal suppression in patients who had been intubated with etomidate compared with those who had been intubated with an alternative agent. Both studies found no difference in mortality associated with etomidate.[83,84] Finally, a retrospective review of pediatric patients with meningococcal sepsis found that patients who were intubated with etomidate, compared with those who received an alternative premedication, had lower cortisol, higher ACTH, and increased 11-deoxycortisol for 24 hours.[85] Because of these known adrenal effects, many experts recommend that etomidate should not be used for intubation in septic shock.[74,86,87] Others argue to continue the use of etomidate because

studies examining mortality associated with etomidate have not found evidence of any increase associated with its use, but all agree that further study is needed.[83,84,88-92]

SUMMARY

Adrenal insufficiency is a serious but often undetected or overlooked medical condition. Patients with adrenal insufficiency are at increased risk of morbidity and mortality due to glucocorticoid deficiency. Acute adrenal insufficiency is a life-threatening condition associated with dehydration and hypotension. Chronic adrenal insufficiency presents with a variety of subtle, vague symptoms. Secondary adrenal insufficiency should be considered in patients with prolonged steroid use, pituitary abnormalities, or midline central nervous system anomalies. Primary adrenal insufficiency should be considered in patients with a family history of autoimmune disease. The classic features of hypotension, hyponatremia, hyperkalemia, and hypoglycemia, although helpful in indicating the diagnosis, may not be present in adrenal insufficiency. Immediate management of adrenal crisis should include aggressive rehydration, correction of hypoglycemia and electrolyte abnormalities, and administration of hydrocortisone (50-100 mg/m^2). In acute illness or in the preoperative setting, patients with known adrenal insufficiency should receive increased doses of glucocorticoids to meet increased metabolic requirements. Relative adrenal insufficiency commonly exists in patients with septic shock. However, the evidence to support the use of hydrocortisone in septic shock is lacking, and the decision to use steroids in septic shock remains controversial.

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