Adrenal Insufficiency in Adults

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KEYWORDS

• Adrenal insufficiency • Cortisol • DHEAS • Stress dose glucocorticoids
• Adrenal crisis

KEY POINTS

- Recognition of signs and symptoms of adrenal insufficiency in both the ambulatory and emergency settings is critical for diagnosis and to reduce mortality from adrenal crisis.
- Dehydroepiandrosterone sulfate (DHEAS) measurement, in addition to morning cortisol levels improves diagnostic ability to assess adrenal insufficiency.
- Peak cortisol cut-off (measured by monoclonal antibody assays) to rule out adrenal insufficiency with the 250-μg cosyntropin stimulation test is likely less than 18 μg/dL.

INTRODUCTION

Etiology/Pathophysiology

The hypothalamic–pituitary–adrenal (HPA) axis is responsible for cortisol (glucocorticoid) production. Adrenal insufficiency (AI) occurs when cortisol secretion is partially or completely impaired. Without adequate treatment, the condition is fatal. There are 3 types of AI: primary, secondary, and tertiary.

Primary AI (PAI) occurs as a result of bilateral adrenal cortex dysfunction or damage directly inhibiting cortisol secretion. In PAI, mineralocorticoid (eg, aldosterone) and adrenal androgen (eg, DHEAS) production are also impaired with rare exception. However, corticotropin-releasing hormone (CRH) production from the hypothalamus and adrenocorticotropic hormone (ACTH) production from the pituitary are intact.

Secondary AI (SAI) results from a pituitary insult that inhibits ACTH production. Tertiary AI is primarily due to medication-induced suppression of hypothalamic CRH production. In both, there is impaired stimulation of the adrenal cortex.

There is no difference in the diagnosis and management of secondary and tertiary AI, so the two will be considered as central AI (CAI). In CAI, the adrenal cortex is intact and in the short-term, its ability to secrete cortisol is also intact. However, if lack of ACTH stimulation persists, the adrenal cortex atrophies, reducing its ability to secrete cortisol until continuous stimulation is restored. Like cortisol, adrenal androgen production, specifically DHEAS, is dominantly regulated by ACTH and is also diminished

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Abbreviations	
ACTH	adrenocorticotropic hormone
AC	adrenal crisis
AI	adrenal insufficiency
CAI	central adrenal insufficiency
CBG	cortisol binding globulin
CRH	corticotropin-releasing hormone
CST	cosyntropin stimulation test
DHEAS	dehydroepiandrosterone sulfate
GC	glucocorticoid
GST	glucagon stimulation test
HCP	health care providers
HIV	human immunodeficiency virus
HPA	hypothalamic–pituitary–adrenal
ITT	insulin tolerance test
IV	intravenous
PAI	primary adrenal insufficiency
SAI	secondary adrenal insufficiency
VLCFA	very long chain fatty acids

in CAI. Aldosterone production remains intact as it is primarily regulated by the renin-angiotensin system.

The management of PAI is different from CAI in that mineralocorticoid replacement is necessary in addition to glucocorticoid replacement; in CAI, glucocorticoid replacement is sufficient.

The most common cause of PAI in the United States is autoimmune disease, whereas in countries with high rates of infectious disease, it remains tuberculosis. The most common cause of CAI in the United States is medication with the highest percentage of cases due to glucocorticoid use. Additional causes of AI are shown in **Table 1**.

SIGNS AND SYMPTOMS

Chronic

The signs and symptoms of AI are often non-specific and insidious in onset making early recognition challenging. Unfortunately, this can result in diagnosis only when symptoms worsen and/or the patient presents with adrenal crisis, especially in those with PAI. Symptoms and signs of glucocorticoid deficiency in PAI and CAI (undiagnosed or undertreated) include:

- Malaise/weakness, fatigue, anorexia, weight loss, nausea, vomiting, abdominal discomfort, lightheadedness, myalgia/joint pain, fever, and hyperpigmentation (PAI only due to increased production of the prohormone proopiomelanocortin which is cleaved into ACTH and melanocyte-stimulating hormone)
- Lab abnormalities: hypoglycemia, hyponatremia (PAI>> CAI)[a], hypercalcemia (PAI; rare in CAI); less common are anemia, lymphocytosis, eosinophilia

Patients with PAI also have symptoms and signs of mineralocorticoid deficiency:

- Salt craving, hypovolemia/dehydration, postural dizziness, and orthostatic hypotension
- Lab abnormalities: hyperkalemia, hyponatremia

[a] Hyponatremia is depletional in PAI due to lack of aldosterone and sodium retention; it is dilutional in CAI as lack of cortisol inhibits free water excretion via increased vasopressin action.

Table 1
Causes of adrenal insufficiency in adults

Primary Adrenal Insufficiency	Central Adrenal Insufficiency
Acute Onset	
• Hemorrhage (eg, antiphospholipid syndrome treated with blood thinners) • Infarction • Bilateral adrenalectomy	• Pituitary apoplexy • Hemorrhage • Pituitary or hypothalamic surgery • Traumatic brain injury without surveillance
Slow Onset	
Autoimmune	*Autoimmune*
• Isolated • Polyglandular syndromes	• Lymphocytic hypophysitis
Infection	*Tumors/Malignancy/Infection*
• Tuberculosis • Fungal (histoplasmosis, cryptococcosis, coccidiomycosis, and blastomycosis) • Viral (human immunodeficiency virus [HIV], cytomegalovirus)	• Pituitary adenoma • Pituitary carcinoma • Craniopharyngioma • Sellar masses • Infection
Infiltrative	*Infiltrative*
• Metastases • Lymphoma • Sarcoidosis, amyloidosis	• Metastases • Langerhans cell histiocytosis • Sarcoidosis, amyloidosis
Other	*Other*
• Congenital adrenal hyperplasia • Adrenoleukodystrophy (males only) • Drugs	• Traumatic brain injury • Radiation • Drugs

PAI patients often crave salt but do not know to report this. It is important to specifically ask about an intense need to drink pickle juice, vinegar, or consume increased quantities of salty foods, e.g., chips, beef jerky, etc.

Acute

AC is the most severe form of AI and shares symptoms with milder, yet acute episodes of hypoadrenalism, which both need to be recognized and promptly treated. There is no widely accepted definition of AC. The pragmatic definition adopted for clinical assessment defines AC as an acute deterioration in health status associated with hypotension (absolute < 100 mm Hg or relative systolic blood pressure $\geq$20 mm Hg lower than usual) with features that resolve within one to 2 hours after parenteral glucocorticoid administration (ie, marked resolution of hypotension within 1 hour and clinical improvement over 2 hours).[1] The clinical presentation is described below:

- Symptoms: anorexia, nausea, vomiting, abdominal, back and leg pain, severe fatigue and/or weakness, postural dizziness, and confusion
- Signs: abdominal tenderness/guarding, hyperpigmentation (PAI only), pyrexia, hypotension (absolute or relative), and impaired consciousness (delirium, obtundation, and coma)
- Biochemical abnormalities: hyponatremia, hyperkalemia, hypercalcemia, hypoglycemia, neutropenia, lymphocytosis, and eosinophilia

AC manifests when AI is left untreated (eg, new diagnosis) or there is an unmet physiologic need for increased glucocorticoid or mineralocorticoid. This can occur when patients with known AI are exposed to increased stress, for example, infection, trauma, surgery, dehydration, and so on. Vomiting and diarrhea (whether due to gastroenteritis or other causes) is the most common precipitant of AC followed by flu-like illnesses and infections.[2]

Up to 50% of patients with PAI experience AC before diagnosis. Patients with Addison's disease report AC even without an obvious trigger or with milder stresses. Emotional distress is also a reported trigger for AC.[3] Unfortunately, AC and the milder forms of acute AI are underrecognized and thus inappropriately managed, leading to premature mortality of AI patients.[2]

DIAGNOSIS

The objectives of HPA axis evaluation are to: (1) confirm low cortisol secretion, (2) determine if primary or central, and (3) determine underlying etiology.

Basal and dynamic tests to confirm low cortisol secretion are described in the sections below. Many of the tests are nuanced and not highly sensitive or specific. The pretest probability of the patient's risk of AI is critical to guide result interpretation. There should be a low threshold to perform additional testing if clinical suspicion and/or patient symptoms persist despite normal initial testing.

Cortisol and Dehydroepiandrosterone Sulfate (DHEAS)

Cortisol secretion follows a diurnal rhythm with the highest levels produced in the morning between 0600 and 0900 followed by a gradual decrease during the day, reaching its nadir between 2300 and 2400. Cortisol secretion is not continuous but intermittent and pulsatile throughout the day. For this reason, random serum total cortisol levels are not recommended as a screening tool for AI. A morning serum cortisol better reflects peak endogenous activation of the HPA axis in the unstressed patient.

Physiologic variability in levels can also make morning cortisol levels difficult to interpret as there is significant overlap between patients with known AI and patients with an intact HPA axis.[4] In this context, deficiencies of CRH or ACTH are frequently partial, resulting in varying levels of cortisol production. Although assay specificity for cortisol has increased, this improvement has not altered the lower limit of screening cortisol thresholds used to prompt additional evaluation. Most studies report that cortisol levels less than 5 μg/dL suggest the need for additional AI evaluation and levels less than 3 μg/dL as strongly suggestive if not diagnostic of AI.[5,6]

Interpretation of the morning cortisol level should consider possible confounders such as altered cortisol binding globulin (CBG) levels, regular use of inhaled corticosteroids, which can lower morning cortisol levels but not cause clinically significant AI; or use of biotin (elevates cortisol in biotin-streptavidin assays, eg, Roche assays) supplements.

At this point, it is prudent to discuss DHEAS in AI screening. In 2003, Nasrallah and colleagues highlighted the value of DHEAS in AI screening in a prospective study of 103 pituitary macroadenoma patients.[7] All patients with an abnormal HPA axis (defined as a serum cortisol response < 18.5 μg/dL in an insulin tolerance test (ITT) and/or morning serum cortisol < 3 μg/dL) had low age-matched and gender-matched DHEAS levels. The investigators suggested that a DHEAS level greater than 65 μg/dL was strongly indicative of an intact HPA axis.

Similarly, Han and colleagues demonstrated that patients with an indeterminate baseline cortisol of 5 to 9.9 μg/dL but DHEAS ≥60 μg/dL (regardless of age and gender

matched values) were unlikely to have AI and do not require further testing unless strong clinical suspicion is present.[8]

Like cortisol, adrenal androgens including DHEAS are under dominant regulation by ACTH and almost exclusively produced by the adrenal cortex with minimal contribution by the testes and ovaries. DHEAS values decrease in PAI because of adrenal cortex destruction and in CAI due to loss of ACTH stimulation of the adrenal cortex.

DHEAS levels have a long half-life of 10 to 20 hours, do not follow a diurnal rhythm, and are not affected by male or female hypogonadism.[7–9] Loss of ACTH stimulation results in loss of adrenal androgen secretion before loss of cortisol secretion, thus it may be an early marker for AI.[9]

Factors that lower DHEAS levels:

- Aging: levels decline with age especially in those older than 65 years
- Glucocorticoid (GC) exposure (especially within last year)
- Chronic illness

Factors that raise DHEAS levels

- Hyperprolactinemia
- DHEA supplement use

In summary, initial screening tests for adrenal insufficiency include a morning cortisol and a DHEAS level. If the cortisol is $\geq$10 μg/dL or is 5 to 9.9 μg/dL with a corresponding DHEAS $\geq$60 μg/dL the patient is unlikely to have AI. Further testing is not needed unless clinical suspicion remains high.[8]

Special Consideration: Autoimmune PAI is a specific clinical situation to consider. In the assessment of autoimmune PAI, it is important to be cognizant of the stages of disease. At first, patients may have negative autoimmune adrenal antibodies and normal cortisol testing. As the disease progresses, a rise in plasma renin activity (not low cortisol) is the first abnormal lab result to manifest. This is eventually followed by abnormal cortisol testing and a rise in ACTH levels. Clinical suspicion and regular follow up are necessary for timely diagnosis.[10]

Cosyntropin Stimulation Tests

If initial clinical and biochemical screening prompts additional evaluation, the 250-μg cosyntropin stimulation test (CST) is conducted to confirm a diagnosis of AI. The test is convenient to perform in most medical offices and is minimally invasive. A baseline cortisol (time 0) is drawn, immediately followed by cosyntropin (ACTH$^{1–24}$) injection (intravenous (IV) or intramuscular injection),[11] followed by repeat cortisol levels drawn at 30 and 60 minutes after injection.

The test was originally performed with a 250-μg dose;[12] however, concerns about supraphysiologic ACTH levels and inability to diagnose mild or recent onset AI led investigators to create the 1 μg dose. Several studies have investigated the diagnostic performance of both tests, concluding that neither test has high sensitivity or specificity nor, is one superior to the other.[13] The 1-μg dose faces challenges as it requires manual dilution of the 250-μg vial and has high false positive rates in the afternoon.[14] In contrast, cosyntropin is packaged in a 250-μg vial making its one time use simple and the test can be performed any time of day.[14]

The 250-μg CST is a robust confirmatory test when performed in the proper clinical context.[15] In CAI, it takes at least 6 weeks for the adrenals to atrophy from lack of ACTH stimulation such that they will not respond to cosyntropin. Testing should occur

at least 6 weeks after the insult, with initiation of earlier glucocorticoid replacement if clinically indicated.

However, even when implemented properly, the CST can produce false negative results in CAI diagnosis.[7,9,16] Additional clinical and laboratory investigation should be considered if the patient is unwell or clinical suspicion remains, for example, presence of additional pituitary deficiencies including low insulin-like-growth factor (IGF)-1; persistent hyponatremia, etc.

In older, fluorometric or polyclonal antibody immunoassays, peak cortisol levels less than 18 μg/dL during the 250-μg CST diagnosed AI. Newer monoclonal antibody cortisol assays measure cortisol with higher specificity, with values approximately 25% to 30% lower than older assays and have excellent correlation with LC-MS/MS, the gold standard in steroid measurement.[17–21] Accordingly, multiple studies recently investigated new diagnostic cortisol cut-offs for AI reporting peak cortisol cut-offs from 12.6 μg/dL-14.7 μg/dL. Different cut-offs are reported for 30 and 60 minutes and it is not clear if relying on the 30 min value alone is sufficient to diagnose AI.

While it is highly probable that the cortisol threshold to diagnose AI is less than 18 μg/dL with the newer assays, it is not clear which level $\geq$12.6 μg/dL to use. Clinicians need to know which assay is used at their institution. This uncertainty highlights the importance of pretest probability of diagnosis and adjunctive testing, for example, DHEAS levels. At this author's institution, a peak cortisol cut-off of less than 15 μg/dL is used for diagnosis (unpublished data).

Free Cortisol

Free cortisol measurement in routine HPA axis evaluation is not necessary but may be a better alternative to evaluate AI in conditions with known protein (CBG and albumin) abnormalities (**Table 2**). Of importance is that albumin is not a reliable indicator of CBG abnormalities, particularly in critically ill patients and women using estrogen therapy.[22]

A free cortisol cut-off of approximately 0.9 μg/dL (with or without ACTH stimulation) has been reported to predict a total cortisol of 18 μg/dL in noncritically ill patients.[22–24] In cases where AI is suspected and/or testing is indeterminate, it is best to treat with glucocorticoids until reliable testing can be performed.

Salivary cortisol is an accurate reflection of serum free cortisol and is gaining more attention in the assessment of AI in the outpatient setting. Salivary cortisol measurement is noninvasive, convenient and simple to perform, stable at room temperature for several days, independent of CBG levels or salivary flow rate, and when measured by LC-MS/MS is free from cross-reactivity by other glucocorticoids.

Although there are limited data, an 8 AM cut-off of less than 0.04 μg/dL was reported to diagnose AI.[25,26] Data on ACTH-stimulated peak salivary cortisol values to rule out AI are limited and not validated at this time.[27–29]

Table 2
Factors that affect cortisol binding globulin levels

Increase cortisol binding globulin	Decrease cortisol binding globulin
• Oral estrogens	• Cirrhosis
• Pregnancy	• Ethanol
• Selective estrogen receptor modulators	• Hyperthyroidism
• Clomiphene	• Nephrotic syndrome
• Mitotane	• Exogenous glucocorticoids
	• *SERPINA6* mutations
	• Malnutrition
	• Prolonged critical illness

Metyrapone Test

The metyrapone test is a single dose, overnight test to evaluate the HPA axis. Metyrapone is an oral medication that blocks cortisol production by inhibition of the 11β-hydroxylase enzyme, the last step in cortisol synthesis (11-deoxycortisol->cortisol). A dose of 30 mg/kg (up to 3 g) is given with food at midnight and measurements of ACTH, serum cortisol, and 11-deoxycortisol are taken the next morning between 07:30 and 09:30.[30,31]

Metyrapone prevents the early morning rise in cortisol. Reduced cortisol levels stimulate a rise in ACTH levels and subsequent stimulation of steroidogenesis resulting in a build-up of steroid precursors, including 11-deoxycortisol, upstream of the block. A serum cortisol less than 5 μg/dL is required to confirm adequate 11β-hydroxylase inhibition. If confirmed, an 11-deoxycortisol level greater than 7 μg/dL suggests an intact HPA axis.

ACTH levels to confirm SAI is suggested by a lesser-than-3x rise in levels; however, this is not validated and should be interpreted with caution.[32]

Metyrapone testing is safe in the ambulatory setting in patients with a low to moderate likelihood of AI. Adverse effects include signs and symptoms of AI: low blood pressure, nausea, vomiting, abdominal discomfort or cramping, and muscle and joint pain. Advise patients to go to the emergency room if necessary. In patients with possibly severe AI, metyrapone testing is not advised.

Metyrapone testing is helpful in diagnosing CAI if a patient has passed the CST and clinical concern remains. Limited availability and high cost prevent its frequent use. Metyrapone is available through specialty pharmacies: https://metopirone.com/home-hcp/accessing-metopirone.

Insulin Tolerance Test

The ITT has long been considered the gold standard test for evaluating the HPA axis. IV insulin (0.1 unit/kg) is administered to induce profound hypoglycemia, which stimulates a counter-regulatory response: HPA axis activation stimulating CRH, ACTH, and, ultimately, cortisol secretion. Cortisol secretion usually does not rise until glucose values are below 70 mg/dL and is maximally stimulated at levels of $\leq$45 mg/dL. Cortisol rises significantly as ACTH levels rise from undetectable to approximately 75 to 100 pg/mL, at which point they plateau regardless of further increases in ACTH. ACTH levels are reported to rise to a peak of 134 $\pm$ 12 pg/mL during the ITT, similar to levels seen in response to severe stress, hence the value of the ITT to predict HPA axis integrity.[4] A peak cortisol value of less than 18–20 μg/dL (older assays) is diagnostic of AI. More recently a cortisol value of less than 12.6 μg/dL measured by the newer Roche II monoclonal antibody assay diagnosed AI.[4,18]

Use of the ITT has fallen out of favor, as it is resource-intense, requires medical supervision, is uncomfortable for the patient, and is contraindicated in groups with cardiovascular or cerebrovascular disease or those with convulsion disorders.

Glucagon Stimulation Test

Primarily used to diagnose growth-hormone deficiency, the glucagon stimulation test (GST) can also evaluate the HPA axis by causing insulin-induced hypoglycemia. GST is infrequently used as a test to diagnose AI as it has the same drawbacks as the ITT.

Additional Tests

Adrenocorticotropic hormone

Morning ACTH levels determine the etiology of AI in the setting of confirmed hypocortisolism. Plasma ACTH is drawn with screening, morning cortisol and DHEAS for practical reasons but is not required for initial screening to establish hypocortisolism. If

ACTH is at or above the upper limit of normal, PAI is likely. Levels at or below the lower end of the reference range (<20 pg/mL) suggest CAI. Note that ACTH needs to be drawn into a chilled tube/on ice as it otherwise degrades rapidly, resulting in a falsely low value.

Adrenal antibodies and very long chain fatty acids

Measurement of 21-hydroxylase adrenal antibodies can confirm an autoimmune etiology in PAI cases. However, the absence of antibodies does not rule out PAI. Very long chain fatty acids (VLCFA) should be checked in all males with PAI to assess for the rare X-linked recessive disorder, adrenoleukodystrophy. The levels are elevated due to defective transport of VLCFA into peroxisomes in this disorder.

DRUGS AND ADRENAL INSUFFICIENCY

GC use is by far the most common cause of drug-induced AI. At least 1% of the population, and greater in the elderly population, are prescribed glucocorticoids to treat numerous conditions spanning all medical specialties.[33] The incidence of GC-induced AI is highest with intra-articular GC which is greater than oral GC, which in turn is greater than inhaled or intranasal GC.

Generally, long-term exposure to supraphysiologic doses of GCs (>15–25 mg hydrocortisone, 4 to 6 mg/day prednisone, 3 to 4 mg prednisolone, 0.25 to 0.5 mg dexamethasone for >3–4 weeks) suppresses the HPA axis. Recent use of multiple GC formulations, regular use of high-dose inhaled or extensive topical GCs, and intra-articular GC injections also put patients at risk of CAI.[33] GC potency, duration of treatment, route of administration, and individual glucocorticoid receptor responsiveness all contribute to a patient's individual risk of developing AI and recovery time. AI arises when GCs are abruptly stopped, leaving the patient without exogenous glucocorticoid *and* without their own inability to produce cortisol because of a suppressed HPA axis.

Recent guidelines recommend that, in general, patients on or tapering off of GCs for nonendocrine conditions do not need evaluation by an endocrinologist. They also recommend that GCs need not be tapered if the therapy is less than 4 weeks, irrespective of dose. In this circumstance, GCs can be stopped without HPA axis testing, as there is low concern for AI.[33]

If evaluation is required, a morning cortisol level greater than 10 μg/dL (assuming no protein abnormalities and not under major stress) suggests a recovered HPA axis. If the level is less than 10 μg/dL consider repeating an AM cortisol monthly until it is clinically appropriate to discontinue glucocorticoids and/or perform an ACTH stimulation test. DHEAS is unlikely to be useful to assess recovery as it suppresses with GC use and has a variable, often long, recovery time.

Other medications that can cause AI are shown in **Table 3**.

Table 3
Drug-induced adrenal insufficiency

Primary adrenal insufficiency	Central adrenal insufficiency
• Antifungals (ketoconazole, itraconazole, fluconazole, and posaconazole) • Abiraterone acetate • Treatments for hypercortisolemia: levoketoconazole, mitotane, metyrapone, osilodrostat, and mifepristone • Heparin	• GC discontinuation • Opioids including methadone • Megestrol acetate • Medroxyprogesterone acetate • Supplements containing GC
PAI and CAI: Immunotherapies (ipilimumab, nivolumab, and pembrolizumab)	

TREATMENT OF ADRENAL INSUFFICIENCY

All patients with AI require physiologic GC replacement, as AI is fatal if left untreated. The goals of treatment are to optimize the patient's quality of life at the lowest GC dose possible that avoids undertreatment while also avoiding overtreatment.

The average adult cortisol production rate is approximately 5 to 10 mg/m^2 per 24 hours. This has translated to an average physiologic replacement dose of 10 to 12 mg/m^2/day (hydrocortisone 15–25 mg per day), which is a bit higher to account for absorption variability and for caution. A standard starting regimen is to take two-third dose on waking and one-third dose in the afternoon, preferably before 5 PM. Hydrocortisone is bioidentical to cortisol and is the preferred treatment choice for AI patients with the least risk of overtreatment. Prednisone and prednisolone (generally interchangeable) are acceptable options understanding their slightly higher potency compared to hydrocortisone. Dexamethasone is 25 to 50 times more potent than hydrocortisone and is avoided as physiologic GC replacement as the risk of overtreatment is high.

Several studies examined the effectiveness of different dosing calculations, for e.g., weight versus body surface area, different regimens, e.g., once, twice or thrice daily dosing, and use of different GCs without conclusive evidence that any one regimen is more effective than the other.[34,35]

While the above regimen is suggested, it is not optimal for all AI patients and individualization is needed. Most regimens do not mimic steroid circadian rhythm or HPA axis response to stress. There are no labs to guide *adequate* therapy as cortisol and ACTH levels do not appropriately reflect sufficiency. Assessment of ongoing signs/symptoms of AI or of GC excess (weight gain, glucose intolerance, hypertension, bone loss/fractures, and so on) along with how the patient feels and functions guides therapy. For example, patients may prefer once daily or thrice daily dosing, feel better with prednisone versus hydrocortisone or perform best with both in split doses.

Consideration should also be given to drugs or absorption issues that can interfere with hydrocortisone metabolism and prompt dose adjustment (**Table 4**).

PAI patients also need replacement with a mineralocorticoid to replace aldosterone deficiency. Fludrocortisone 100 μg (50–250 μg) once daily is usually sufficient. The dose can be increased as needed for exposure to excess heat and humidity or any condition putting the patient at increased risk of dehydration, which can quickly become a fatal course for these patients. Similarly, keeping salt tablets on hand is useful to prevent dehydration and AC.

Women with PAI also experience androgen deficiency and may need replacement for an acceptable quality of life. Women with low libido, depressive symptoms, and/or lack of energy despite adequate GC and MC replacement for at least 6 months can try DHEA supplementation (over the counter) and discontinue if no effect. Serum DHEAS levels drawn before the next dose of DHEA can be used to guide therapy aiming for the midnormal range.[37]

Table 4
Drug interactions and interference with hydrocortisone[36]

Accelerate metabolism by induction of CYP3A4	Impair metabolism by inhibition of CYP3A4
Phenobarbital	Aprepitant/fosaprepitant
Phenytoin/fosphenytoin	Azole antifungal drugs
Carbamazepine	Ritonavir

(*continued on next page*)

Table 4
(continued)

Accelerate metabolism by induction of CYP3A4	Impair metabolism by inhibition of CYP3A4
Primidone	Fluoxetine
Rifampin	Diltiazem
Rifapentine	Cimetidine
Ethosuximide	
Pioglitazone	
Drugs that interfere with hydrocortisone absorption	
Cholestyramine, Colestipol	

Note: The listed drugs can also affect the metabolism of dexamethasone and prednisone. This list is not all-inclusive of potential steroid drug interactions. Additional data can be found at https://medicine.iu.edu/internal-medicine/specialties/clinical-pharmacology/drug-interaction-flockhart-table.

STRESS DOSING/SICK DAY RULES AND MANAGEMENT OF ADRENAL CRISIS

Increased GC dosing (*stress dosing*) is imperative for AI patients when exposed to any stress, as they cannot mount this response on their own. Stress dosing allows for an appropriate response to stress and can prevents AC (**Table 5**). Patients can increase their daily, oral GC doses, self-administer an injectable GC (e.g. hydrocortisone), or go to a healthcare facility for intravenous GC treatment depending on the severity of illness (**Table 5**).

Table 5
Stress dosing in illness

Fever >38°F	Double the daily hydrocortisone dose until recovery, then return to standard dose within 1–2 d
Fever > 39°F	Triple the daily hydrocortisone dose until recovery, then return to standard dose within 2 d
Gastroenteritis with vomiting and/or diarrhoea	Early parenteral hydrocortisone (100 mg subcutaneously or intramuscularly); to be repeated after 6–12 h
Severe infection (eg, pneumonia/with altered cognition)	Early parenteral hydrocortisone (100 mg subcutaneously or intramuscularly); to be repeated after 6–12 h (49) until recovery
Major emotional or mental stress (eg, death of a close relative, major university examination)	Addition of 10–20 mg hydrocortisone to the standard replacement dose
Exhaustive strenuous exercise	Add 10 mg hydrocortisone 30–60 min before the exercise

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There are various iterations of stress dosing for procedures in the literature and Table 6 reflects a synthesis of these guides, with not one guidance being more correct than the other.[33,38] There are limited controlled data to demonstrate superiority of high versus moderate stress doses. Lower doses, that is, hydrocortisone 25 mg IV every 6 hours from start of surgery, are also reported as effective.[39] The most important point is that the clinician and the patient are aware of when stress dosing is needed and it is implemented.

Table 6
Stress dosing guidelines for procedures[33,38]

Procedure	Preoperative Needs	Postoperative Needs
Minor procedure	Usually not required	Extra dose (eg, 20 mg hydrocortisone) if symptoms persist
Dental procedure	Extra morning dose 1 h before surgery	Double oral dose × 24 h, then return to normal dose
Minor surgery including any procedure requiring local anesthesia including dental surgery	Hydrocortisone 25–75 mg/24 h (usually 1–2 d)	Continue increased dose if unwell after procedure until clinically stable, then return to normal dose
Major surgery with general anesthesia, trauma, labor and delivery, caesarian section, or disease that requires intensive care	Hydrocortisone 100 mg IV bolus at induction, followed by hydrocortisone, 50 mg IV bolus every 6 h, or alternatively, a continuous infusion of hydrocortisone of hydrocortisone, 200 mg, over 24 h	Resume oral glucocorticoids at increased dose for 48 h; then resume normal dose. If complications, maintain increased oral or IV dosing as clinically appropriate

If a patient presents in AC, treatment is according to Table 7.

Table 7
Adrenal crisis treatment[38]

Treatment	Dose/Procedure
Hydrocortisone	100 mg bolus given immediately followed by 200 mg/day as continuous infusion or frequent intravenous (or intramuscular) boluses (50 mg) every 6 h
IV substitution of fluids	1000 mL of 0.9% sodium chloride during the first 60 min, further fluid administration (0.9% sodium chloride) guided by individual patient needs as assessed clinically or by central venous pressure; frequent hemodynamic monitoring to avoid fluid overload; measurement of serum electrolytes
Depending on the severity of the crisis and on the intercurrent illness	Admission to the intensive care or high dependency unity; low-dose heparin; antibiotic treatment

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AC is still a significant cause of death in patients with AI despite the availability of effective prevention strategies.[1] Patient and family/friend/caregiver education on stress dosing, signs and symptoms of AC, and how to respond to signs of clinical deterioration are critical to reduce morbidity and mortality. Please note that once AI patients start to clinically deteriorate, brain fog and confusion can prevent them from being able to self-administer an injection, hence the importance of another knowledgeable administrator.

Equally important is awareness of the diagnosis by healthcare providers (HCPs), especially first responders and emergency medical personnel. Patients report HCP withholding of glucocorticoid treatment due to concern for adverse effects of glucocorticoids or disbelief regarding diagnosis even with medic alert jewelry or wallet card on hand.[40]

Patient advocate groups provide immense support, education, and tools for patients and HCPs, for example, National Adrenal Diseases Foundation (NADF.us).

Emergency Kit for Adrenal Insufficiency

AI patients should keep an emergency kit with them at all times.

- Wallet card/identification stating that the patient has AI, primary health care provider/endocrinologist name and phone number
- Medic Alert bracelet or necklace stating: *Adrenal Insufficiency—needs steroids*!
- Extra hydrocortisone tablets
- Extra fludrocortisone or salt tablets (PAI)
- Injectable hydrocortisone with the appropriate syringes and needles, alcohol pad
  - Patients/family members/friends can watch online video tutorials on how to administer the injection
  - Administer by subcutaneous or intramuscular injection, whatever is easiest for the patient or their caregiver

SUMMARY

Adrenal insufficiency is a manageable disease once diagnosed. Diagnosis requires awareness of signs and symptoms and a low threshold to investigate if it is considered. Patients and their families/friends/caregivers need education on AI management, stress dosing, and AC prevention. Despite availability of basic therapies, development of replacement dosing to follow the circadian rhythm will allow for improved quality of life for many. Similarly, development of an autoinjector for emergency hydrocortisone delivery rather than the current vial/syringe system could provide significant relief for and improve mortality rates in those with AI.

CLINICS CARE POINTS

- Measure morning cortisol and DHEAS (ACTH optional but helpful) as initial AI screen.
- If screening tests do not rule out AI, proceed to CST. If CST is a possible false negative, consider metyrapone testing.
- Be aware of lowered diagnostic cortisol cut-offs with CST.
- Be aware of confounders to cortisol measurements: oral estrogen use, nasal inhalers, interfering medications, supplements containing biotin and/or glucocorticoids (usually unbeknownst to patient).

- AC is manageable if it is considered in the differential, especially in the emergency room. Administer stress dose glucocorticoids without confirmation of disease if needed. The risk of undertreatment is greater than the short-term risk of high dose glucocorticoids.[37]
- Provide AI/AC education to patients, friends/family/caregivers, healthcare providers, first responders, and emergency room personnel.

DISCLOSURE

Dr S.B. Abraham provides confidential consulting services through Emerald Crescent LLC to certain clients in the pharmaceutical industry. All treatments and therapies discussed are based on publicly available evidence and peer-reviewed literature.

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