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# Primary adrenal insufficiency in adults: When to suspect, how to diagnose and manage

## ABSTRACT

Primary adrenal insufficiency is rare but serious; it puts patients at risk of acute decompensation and adrenal crisis due to insufficient cortisol and aldosterone production. Further, its diagnosis is often delayed, or it is mistaken for secondary adrenal insufficiency, which can have life-threatening consequences. Early recognition and appropriate treatment can greatly improve patient outcomes and quality of life.

## KEY POINTS

Unlike secondary adrenal insufficiency, primary adrenal insufficiency requires lifelong replacement of both glucocorticoids and mineralocorticoids, most commonly hydrocortisone and fludrocortisone.

The first step in diagnosing adrenal insufficiency in general is to measure the early-morning cortisol level, looking for a low value. If the result is indeterminate, the next step is to do a cosyntropin stimulation test.

To confirm the diagnosis of primary adrenal insufficiency specifically, one should measure the adrenocorticotrophic hormone level, ideally concurrently with an early morning cortisol level, looking for a high value.

To ensure adherence with lifelong steroid therapy and avoid adrenal crises, patients need adequate and ongoing education about the benefits and side effects of this treatment.

UNTREATED PRIMARY ADRENAL insufficiency is life-threatening because patients can present with sudden decompensation and severe illness, such as adrenal crisis. Yet, the diagnosis is often significantly delayed, or it is misdiagnosed as secondary adrenal insufficiency. Unlike secondary adrenal insufficiency, therapy for primary adrenal insufficiency must include both glucocorticoid and mineralocorticoid replacement. It is important for clinicians to recognize, treat, and adequately counsel affected patients to improve patient adherence and outcomes.

## ■ PRIMARY VS SECONDARY ADRENAL INSUFFICIENCY

Adrenal insufficiency is a heterogeneous group of conditions in which there is a deficit of the main adrenal stress hormone, cortisol. When confronted with a patient who has adrenal insufficiency, it is critical to distinguish whether the insufficiency is primary or secondary because the workup and treatment differ fundamentally.

**Primary adrenal insufficiency** stems from a problem in the adrenal gland itself, and there are deficits of hormones produced at multiple layers of the adrenal cortex: mineralocorticoids from the zona glomerulosa, glucocorticoids from the zona fasciculata, and the sex hormones dehydroepiandrosterone (DHEA), sulfated DHEA (DHEA-S), and androstenedione from the zona reticularis. Therefore, patients with primary adrenal insufficiency require both glucocorticoid and mineralocorticoid

supplementation to survive. Primary adrenal insufficiency is relatively rare, with a prevalence of approximately 100 to 140 per million people in western countries, and it disproportionately affects women between ages 30 and 50.<sup>1-3</sup>

Primary adrenal insufficiency was first described in 1855 by Thomas Addison.<sup>4</sup> He initially dubbed the condition “melasma suprarenale,” but it became known as “Addison’s disease.” Although Addison discovered his eponymous condition by studying a series of patients with adrenal tuberculosis, today the term is used to refer to primary adrenal insufficiency from any etiology (see *Causes of primary adrenal insufficiency*, below).

**Secondary adrenal insufficiency** is characterized by inadequate adrenocorticotrophic hormone secretion stemming from a problem in the pituitary gland or hypothalamus (the latter is sometimes called “tertiary adrenal insufficiency”) or from suppression of the hypothalamic-pituitary-adrenal axis, most often associated with chronic exogenous steroid use. Adrenocorticotrophic hormone is necessary for cortisol and adrenal androgen generation. However, production of the mineralocorticoid aldosterone is unaffected, since it is predominantly and independently regulated by the renin-angiotensin-aldosterone system. Thus, patients with secondary adrenal insufficiency need only glucocorticoid replacement. Secondary adrenal insufficiency is more common than primary, affecting 150 to 280 per million people.<sup>2,3</sup>

### ■ DIAGNOSIS IS OFTEN DELAYED

It takes a high degree of clinical suspicion to recognize and treat primary adrenal insufficiency promptly. Affected patients have higher rates of adrenal crisis and death than those with other forms of adrenal insufficiency, as they have life-threatening deficiencies in both cortisol and aldosterone.<sup>5</sup> The insidious and nonspecific symptoms of primary adrenal insufficiency are often misattributed to psychiatric or gastrointestinal disease.<sup>6</sup> Even once adrenal insufficiency is recognized, primary adrenal insufficiency is often mistaken for secondary, as the latter is roughly 2 to 3 times more prevalent.<sup>1-3</sup> No surprise, then, that observational studies have found an average delay of 3 to 6 months before primary adrenal insufficiency is identified, which can be life-threatening for patients.<sup>6,7</sup>

While many patients with primary adrenal insufficiency ultimately establish care with an endocrinologist, most initially present to clinicians in primary care, emergency medicine, hospital medicine, or other medical specialties. Therefore, it is relevant to review

an approach to the diagnosis, workup, and management of primary adrenal insufficiency in adults for these medical audiences.

### ■ WHEN TO SUSPECT PRIMARY ADRENAL INSUFFICIENCY

Many of the features of primary adrenal insufficiency are nonspecific and overlap with those of adrenal insufficiency from any cause, eg, fatigue, nausea, anorexia, abdominal pain, weight loss, hypotension, hypovolemia with postural dizziness, hyponatremia, and unexplained hypoglycemia. These symptoms may range from mild to life-threatening and may be masked until times of significant stress or illness. Suspect adrenal crisis in any patient who presents with shock out of proportion to the severity of his or her illness, possibly associated with otherwise-unexplained confusion, lethargy, fever, vomiting, or dehydration.

When looking for clinical features to distinguish primary from secondary adrenal insufficiency, consider 2 key factors:<sup>8</sup>

**Symptoms of aldosterone deficiency.** Without sufficient mineralocorticoid production, patients with primary adrenal insufficiency are more prone to significant hypovolemia and hyperkalemia, with more frequent symptoms of salt craving than those with secondary adrenal insufficiency.

**Signs of adrenocorticotrophic hormone excess.** Alpha melanocyte-stimulating hormone is a byproduct of adrenocorticotrophic hormone breakdown, and it has pigmentary action at the melanocortin 1 receptor in melanocytes in skin and mucosa.<sup>8</sup> Therefore, in primary adrenal insufficiency, excess adrenocorticotrophic hormone secretion can lead to skin hyperpigmentation that resembles a long-lasting suntan.

### ■ BIOCHEMICAL EVALUATION

Biochemical evaluation is key to confirming a diagnosis of adrenal insufficiency from any cause.

#### **Low early morning cortisol**

First, there must be evidence of low serum cortisol at its daily peak, around 8 AM. Random cortisol checks, no matter how low, cannot reliably make a diagnosis of adrenal insufficiency. The recommended timing is based on an expected diurnal variation during a normal sleep-wake cycle.

Patients with significantly altered sleep schedules (eg, night shift workers) should have their cortisol levels checked at whatever time they routinely wake up after maintaining a consistent sleep pattern for a

few weeks. Cortisol interpretation becomes even more difficult in hospitalized patients, particularly in the intensive care unit, in part due to sleep disruptions and acute stress associated with illness.<sup>9,10</sup> As a result, there are no recognized cortisol cutoff values for diagnosing adrenal insufficiency in this setting.

Outside the intensive care unit, a morning cortisol value lower than 3 µg/dL in the absence of cortisol-binding globulin deficiency is consistent with adrenal insufficiency and does not require further testing if symptoms are consistent with this diagnosis. Meanwhile, a cortisol value above 13 to 18 µg/dL (depending on the assay used) excludes adrenal insufficiency.<sup>11,12</sup>

There are other common complicating factors to consider when interpreting early morning cortisol levels:

**Variations in binding globulin and albumin.** The cortisol assay measures total cortisol, which includes both free (active) hormone and bound hormone (80% to 90% is bound to cortisol-binding globulin and 10% to 15% is bound to albumin, leaving only 5% to 10% of cortisol active in free circulation). Oral contraceptive pills and other estrogen compounds can increase cortisol-binding globulin and inflate total cortisol levels. Conversely, total cortisol levels are falsely low when albumin levels are below the normal range. In these cases, especially when the albumin level is less than 2.5 g/dL, the free cortisol assay should be used instead.<sup>13</sup> However, delay in getting free cortisol results can limit their clinical usefulness in urgent situations.

**Exogenous steroid therapy.** Cortisol levels are not reliable if patients are receiving exogenous steroids, as these can both decrease the measured cortisol by suppressing the hypothalamic-pituitary-adrenal axis and, conversely, increase the measured cortisol if the assay detects the exogenous steroid. We recommend waiting until the steroid has cleared the system, generally about 24 hours depending on the steroid's duration of action, before testing cortisol levels in these patients.

For patients with indeterminate early morning cortisol values, one should proceed with further testing.

### Cosyntropin stimulation test

If the cortisol value is indeterminate, the next step in confirming a diagnosis of adrenal insufficiency from any cause is to perform a cosyntropin stimulation test. Cosyntropin is a synthetic peptide consisting of the first 24 amino acids of the natural adrenocorticotropic hormone molecule.

To perform the test, 250 µg of cosyntropin is given intramuscularly or intravenously, and cortisol levels are checked at baseline, 30, and 60 minutes.<sup>1</sup> If both the 30- and 60-minute values are below the laboratory's

threshold, the patient has adrenal insufficiency. The test can be done at any time of day but is often done in the morning so that the baseline level meaningfully reflects the daily peak cortisol. It can also be performed using free cortisol levels if the serum albumin level is below the normal range.

Cosyntropin stimulation testing can be done even if the patient is receiving dexamethasone, as this exogenous steroid does not falsely increase the cortisol assay. For this reason, the cosyntropin stimulation test is the main method used to assess residual adrenal function in patients who require uninterrupted steroid therapy. The cutoff for diagnosis varies (< 12.6 vs < 18.0 µg/dL) depending on the cortisol assay used.<sup>1</sup>

A cortisol value exceeding the cutoff at any time point during stimulation testing can be used to exclude adrenal insufficiency. One exception is that stimulated cortisol values can be falsely normal in acute secondary adrenal insufficiency, and this should be suspected in the setting of recent pituitary trauma or surgery.

### DHEA-S testing

Recently, researchers have been looking at the value of DHEA-S testing, as this hormone has a long half-life and does not have diurnal variation. One method involves calculating the DHEA-S ratio by dividing the DHEA-S level by the lower limit of an age- and sex-specific reference range. Charoensri et al reported that a DHEA-S ratio greater than 1.78 was 100% sensitive for ruling out adrenal insufficiency.<sup>14</sup> Additionally, Suresh et al reported that a DHEA-S level less than 25 µg/dL confirms adrenal insufficiency, while a level greater than 100 µg/dL excludes it, with good sensitivity and specificity.<sup>15</sup> If the DHEA-S level is between 25 and 100 µg/dL, ie, indeterminate, the next step would be cosyntropin stimulation testing.

### Other tests and findings

Other tests for adrenal insufficiency such as the metyrapone stimulation test, the low-dose cosyntropin stimulation test, or the insulin tolerance test can be used but should be performed and interpreted with the assistance of an endocrinologist.<sup>16</sup>

Once a diagnosis of adrenal insufficiency is made, glucocorticoid therapy should be initiated without delay. Even if results are not back, if clinical suspicion for adrenal insufficiency is high, steroids should be started once laboratory samples are drawn.

Additional testing may be needed to distinguish between primary and secondary adrenal insufficiency. It is a common misconception that the cosyntropin stimulation test necessarily diagnoses primary

TABLE 1

**Congenital and inborn causes of primary adrenal insufficiency**

Category and cause	Key features <sup>a</sup>
<b>Congenital adrenal hyperplasia<sup>1</sup></b>	21-Hydroxylase deficiency
	Most common subtype
	Classic variant causes deficiency of both cortisol and aldosterone
	Can also cause virilization in females due to accumulation of dehydroepiandrosterone metabolites
	11-Beta-hydroxylase deficiency
	Accumulation of aldosterone precursor 11-deoxycorticosterone results in hypertension and hypokalemia
	3-Beta-hydroxylase deficiency
	Lack of dehydroepiandrosterone conversion to testosterone causes ambiguous genitalia in boys
<b>Other enzymatic abnormality<sup>17</sup></b>	Aldosterone synthase deficiency
	Isolated mineralocorticoid deficiency
<b>ACTH resistance<sup>23</sup></b>	Deficiency of P450 side-chain cleavage enzyme
	Slows the rate-limiting step in cortisol synthesis
	Familial glucocorticoid deficiency type 1
<b>Adrenoleukodystrophy<sup>23</sup></b>	Tall stature, isolated deficiency of glucocorticoids, and generally normal aldosterone production
	3A (Allgrove, AAA) syndrome
<b>Congenital adrenal dysgenesis<sup>1</sup></b>	Achalasia, Addison disease, alacrimia, AAAS gene mutation
	Accumulation of very long chain fatty acid in adrenal cortex
<b>Others (rare)<sup>1,17,23</sup></b>	Inhibited response to ACTH; X-linked recessive disorder associated with neurologic deficits that predominantly affects males and typically presents in adolescence
	Congenital but can also be secondary to ACTH deficiency
	Hypotrophy of adrenal cortex, adrenal insufficiency, hypogonadism, especially in males due to reduction in adrenal androgens
	Wolman disease
	Lysosomal acid lipase deficiency that results in accumulation of fat and diffuse punctate adrenal calcification causing adrenal insufficiency
	Very poor prognosis
	Abetalipoproteinemia
	Fat malabsorption results in lack of cholesterol to make steroids
	Mitochondrial disorders
	External ophthalmoplegia, retinal degeneration, cardiac conduction defects

<sup>a</sup>Not all listed primary adrenal conditions necessarily present with both glucocorticoid and mineralocorticoid deficiency.

AAA = achalasia, Addison disease, alacrimia; ACTH = adrenocorticotrophic hormone

disease; even in secondary disease the adrenal gland has a slow, suboptimal response to synthetic exogenous adrenocorticotrophic hormone due to a chronic lack of endogenous stimulus. The adrenocorticotrophic hormone level is the most reliable way to differentiate primary from secondary adrenal insufficiency. Ideally it should be measured concurrently with an early morning cortisol. Adrenocorticotrophic hormone levels greater than 2 times the upper limit of normal at any time of day are consistent with a diagnosis of primary adrenal insufficiency.<sup>1</sup>

Additional laboratory findings that can increase suspicion for a diagnosis of primary adrenal insufficiency include elevated renin, low aldosterone, low sodium, and high potassium.<sup>1</sup>

Once primary adrenal insufficiency has been diagnosed, the next step is to identify the cause.

## ■ CAUSES OF PRIMARY ADRENAL INSUFFICIENCY

Autoimmune destruction of the adrenal gland is the most common cause of primary adrenal insufficiency in the western world, responsible for up to 90% of cases.

**TABLE 2**  
**Acquired causes of primary adrenal insufficiency**

Category and cause	Key features <sup>a</sup>
<b>Autoimmune (most common)</b>	Sporadic (from affected 21-hydroxylase enzyme)
	40% of autoimmune cases, <sup>12</sup> common in patients age 30–50 <sup>25</sup>
	Autoimmune polyglandular syndrome type 1 <sup>b</sup>
<b>Infection</b>	Hypoparathyroidism, chronic mucocutaneous candidiasis, Addison disease, other autoimmune diseases such as pernicious anemia, alopecia (5% to 10%) <sup>17</sup>
	Autoimmune polyglandular syndrome type 2 <sup>b</sup>
	Autoimmune thyroid disease, type 1 diabetes, vitiligo, premature gonadal failure (60%) <sup>17</sup>
<b>Injury</b>	Tuberculosis
	Most common cause in countries where tuberculosis is prevalent An extra-adrenal primary lesion is usually present Antitubercular medications do not reverse destruction <sup>18</sup>
	Disseminated histoplasmosis, paracoccidioidomycosis, human immunodeficiency virus or acquired immunodeficiency syndrome, cytomegalovirus, tertiary syphilis
<b>Metastases</b>	Bilateral adrenal hemorrhage due to sepsis
	Classically with disseminated meningococcemia, but can also occur with <i>Pseudomonas aeruginosa</i> , <i>Streptococcus pneumoniae</i> , or <i>Staphylococcus aureus</i> sepsis <sup>19</sup>
	Bilateral adrenal hemorrhage due to anticoagulation
	Rarely occurs with systemic anticoagulation Usually within the first 2 weeks of therapy <sup>20</sup>
	Infarction due to antiphospholipid antibody syndrome
<b>Acquired adrenal dysgenesis</b>	Bilateral venous thrombosis Affects more men than women Antibodies target lipid-rich cells in the adrenal gland <sup>21</sup>
	Physical trauma
	In decreasing order: lung, breast, melanoma, stomach <sup>22</sup>
<b>Iatrogenic</b>	Adrenal glands are prone to metastasis due to relatively rich blood supply Mere presence of metastasis does not cause adrenal insufficiency; severe destruction (> 90%) of the adrenal cortex is necessary
	Secondary to adrenocorticotrophic hormone deficiency; can also be congenital
	Hypotrophy of adrenal cortex, adrenal insufficiency, hypogonadism, especially in males due to reduction in adrenal androgens <sup>1</sup>
<b>Infiltrative</b>	Surgical bilateral adrenalectomy
	Usually performed in the setting of Cushing disease or bilateral pheochromocytoma
<b>Latrogenic</b>	Drugs
	See Table 3
<b>Infiltrative</b>	Hemochromatosis, sarcoidosis, amyloidosis
	Extensive infiltration of adrenal cortex results in dense fibrosis and deficiency of cortisol and aldosterone <sup>24</sup>

<sup>a</sup>Not all listed primary adrenal conditions necessarily present with both glucocorticoid and mineralocorticoid deficiency.

<sup>b</sup>From major histocompatibility complex class II mutations plus environmental triggers such as mental stress, viral infections, drugs.



**TABLE 3**  
**Drugs that can cause primary adrenal insufficiency**

Drug <sup>a</sup>	Use	Mechanism of primary adrenal insufficiency
Mitotane	Adrenolytic adrenocortical carcinoma therapy	Damages adrenal cortex through free radical generation, blocks cortisol production, and alters peripheral conversion of steroids <sup>27</sup>
Etomidate	Anesthetic	Etomidate and metyrapone inhibit 11-beta-hydroxylase and decrease endogenous cortisol synthesis <sup>28,29</sup>
Metyrapone, mifepristone	Cushing syndrome therapy	Mifepristone in high doses blocks the glucocorticoid receptor <sup>28</sup>
Ketoconazole	Antifungal	Inhibits several adrenal enzymes responsible for androgen and cortisol synthesis such as cholesterol side chain cleavage enzyme, 17-alpha-hydroxylase, 11-beta-hydroxylase, and aldosterone synthase <sup>28</sup>
Levoketoconazole	Cushing syndrome therapy	
Rifampicin	Antitubercular	Induce CYP3A4, promote rapid cortisol clearance from the blood <sup>17</sup>
Phenytoin	Antiseizure	
Immune checkpoint inhibitors: ipilimumab (CTLA-4), nivolumab (PD-1), pembrolizumab (PD-1)	Malignancy therapy, most often melanoma	Can cause adrenal antibodies, resulting in destruction of cortex <sup>30,31</sup>  Can also be associated with secondary adrenal insufficiency through hypophysitis
Abiraterone	Prostate cancer therapy	Selectively and irreversibly inhibits 17-alpha-hydroxylase/C17,20-lyase to cause androgen and glucocorticoid deficiency <sup>32</sup>

<sup>a</sup>Not all listed medications causing primary adrenal insufficiency necessarily present with both glucocorticoid and mineralocorticoid deficiency.  
 PD-1 = programmed cell death protein 1; CTLA-4 = cytotoxic T-lymphocyte–associated protein 4.

Based on information from references 1,17,23,27–32.

Other causes include infections (eg, tuberculosis), adrenal hemorrhage or infarction, metastases, surgical resection, and congenital conditions.<sup>17–24</sup> Drug-induced primary adrenal insufficiency is also emerging. Congenital and inborn causes of primary adrenal insufficiency are listed in **Table 1**,<sup>1,17,23</sup> and acquired causes are listed in **Table 2**.<sup>1,12,17–22,24,25</sup>

### Drug-induced primary adrenal insufficiency is on the rise

Drug-induced primary adrenal insufficiency is rapidly increasing in incidence. While mitotane and etomidate have long been known to cause adrenal dysfunction, the advent of immune checkpoint inhibitors and other medications to treat cancer and immune diseases has increased the incidence of iatrogenic adrenal disease. Recognizing adrenal insufficiency in such patients can be challenging, as the symptoms frequently overlap with those of the disease that required the use of that medication in the first place.

A 2022 study of reports received by the US Food and Drug Administration found 56 drugs suspected of causing primary or secondary adrenal insufficiency.<sup>26</sup>

The most common medications that cause primary adrenal insufficiency are listed in **Table 3**.<sup>1,17,23,27–32</sup> Some of these drugs can induce primary adrenal insufficiency by suppressing the adrenal enzyme cascade, while others can induce adrenal antibodies, directly harm the adrenal cortex, or induce cortisol metabolism.

### Practical approach to finding the cause of primary adrenal insufficiency

After excluding clear iatrogenic causes with a patient history and medication list, a stepwise approach is recommended for finding the cause of primary adrenal insufficiency.<sup>1</sup>

**21-Hydroxylase antibody testing.** Since most cases are autoimmune, the recommended workup begins with 21-hydroxylase antibodies. Imaging is not necessary and is relatively nonspecific for a diagnosis of autoimmune primary adrenal insufficiency but may show small atrophic adrenal glands.

When autoimmune disease is identified, it is important to consider other autoimmune diseases that can be associated with primary adrenal insufficiency such as thyroid disease, type 1 diabetes, pernicious anemia, and

celiac disease. The most common patterns are autoimmune polyglandular syndromes 1 and 2. With a sensitivity of approximately 90%, a negative 21-hydroxylase antibody test does not necessarily exclude autoimmune disease in cases with a high clinical suspicion in the absence of another identifiable cause.<sup>2,33</sup>

**Computed tomography.** If 21-hydroxylase antibody testing is unremarkable, a computed tomography scan of the adrenal glands is recommended. Generally, more than 90% of both adrenal cortices must be damaged before the signs and symptoms of primary adrenal insufficiency manifest.<sup>12</sup> Computed tomography is done to look for any overt adrenal infiltration, infection, hemorrhage, malignancy, or injury. A positive result will require further investigation based on the clinical history, physical examination, and suspected cause. For example, QuantiFERON testing should be considered for those at risk for tuberculosis, which remains the second leading cause of primary adrenal insufficiency worldwide.<sup>18</sup>

**17-Hydroxyprogesterone level.** Though other causes of primary adrenal insufficiency are rare, if patients do not have antibodies or computed tomography findings, screening for congenital adrenal hyperplasia is recommended by measuring the 17-hydroxyprogesterone level, looking for elevated values.

**Very-long-chain fatty acids.** In adolescent male patients, consider screening for adrenoleukodystrophy by looking for elevated levels of very-long-chain fatty acids.

Other rare genetic conditions can be tested for based on the patient's phenotype and comorbidities, with the guidance of an expert in genetics. If all workup is unrevealing, then primary adrenal insufficiency is considered idiopathic.

## ■ HOW TO TREAT PRIMARY ADRENAL INSUFFICIENCY

The general approach to treating primary adrenal insufficiency of any etiology is physiologic replacement of necessary glucocorticoids and mineralocorticoids. These medications must be started promptly upon diagnosis, which often occurs in primary care or the hospital. Adherence to medical therapy must be emphasized to prevent serious illness. Further medication titration, surveillance, and consideration of nonessential androgen replacement should take place with an endocrine specialist if available.

### Glucocorticoid replacement with hydrocortisone

The starting dose of hydrocortisone is 15 to 25 mg per day (approximately 8–15 mg/m<sup>2</sup> per day by body surface

area) divided into 2 or 3 doses, given that hydrocortisone is cleared in approximately 8 hours.<sup>1</sup> To mimic the physiologic diurnal variation in cortisol, the recommended dose is higher (10–15 mg) in the morning and lower (5–10 mg) in the afternoon, 6 to 8 hours later. The body's natural glucocorticoid production is low during sleep, but an evening dose (2.5–5 mg) can be considered in patients who feel symptoms of adrenal insufficiency overnight.

Newer, modified-release hydrocortisone formulations contain both immediate- and sustained-release components and are taken once daily. This improves medication adherence and is thought to better match physiologic cortisol variability. Initial randomized controlled trials demonstrated improvements in weight, glucose tolerance, blood pressure, and quality of life with modified-release hydrocortisone.<sup>34,35</sup> These formulations are not widely used yet and are undergoing ongoing study.

**Other glucocorticoid medications.** Prednisone and prednisolone (3–5 mg/day) are 4 times more potent than hydrocortisone and can be taken once daily. While there is no significant medical evidence that one steroid formulation is better than another, hydrocortisone is easier to titrate to avoid the consequences of excessive long-term steroid exposure.<sup>36</sup> The risks of long-term excess steroid exposure are even higher with dexamethasone, which is 20 times more potent than hydrocortisone. Forss et al<sup>37</sup> surveyed 1,245 patients with adrenal insufficiency worldwide and reported that 75% were receiving hydrocortisone, 11% were on prednisone or prednisolone, 6% were on cortisone acetate, 4% were on dexamethasone, and the rest were on other drugs.

Once therapy has begun, laboratory cortisol levels are no longer useful for guiding dose adjustment. Instead, the need for glucocorticoid titration is determined by clinical response. Fatigue, nausea, weakness, anorexia, weight loss, hypoglycemia, hypotension, or the occurrence of an adrenal crisis suggest inadequate glucocorticoid replacement, and the dose should be increased. Cushingoid features (round facies, purplish striae, easy bruising, dorsocervical fat pad, central obesity), weight gain, fatigue, proximal muscle weakness, bone loss, hypertension, hyperglycemia, and an increased infection rate are evidence of cortisol excess. Fear or evidence of these symptoms is a common reason for steroid nonadherence.<sup>38</sup>

Both excess and suboptimal glucocorticoid therapy cause clear harms. Thus, providers should monitor for early symptoms and work with patients to aim for the lowest replacement steroid dose that is sufficient.

### Mineralocorticoid replacement

The starting dose of mineralocorticoid replacement is fludrocortisone 50 to 100  $\mu\text{g}$  daily, titrated to a range of 50 to 300  $\mu\text{g}$  daily.<sup>39</sup> Clinical features are used to assess the adequacy of therapy. Patients should be asked about salt craving or dizziness and screened for orthostatic hypotension and laboratory abnormalities such as hyperkalemia or hyperreninemia, which suggest mineralocorticoid underreplacement.

Conversely, signs of volume overload such as hypertension or hypokalemia and hyporeninemia can be a clue for overreplacement. Patients who develop hypertension while on fludrocortisone can decrease the dose but should not stop fludrocortisone therapy altogether. Other antihypertensive agents can be started for additional blood pressure control when the lowest fludrocortisone dose is already in use.

Some glucocorticoids at high doses (hydrocortisone > 20 mg and prednisone or prednisolone > 50 mg) can act at the mineralocorticoid receptor with approximate equivalent strength as fludrocortisone 100  $\mu\text{g}$ .<sup>40</sup> Fludrocortisone can be held in these circumstances but must be promptly resumed when glucocorticoid doses are lowered below these thresholds. In contrast, dexamethasone does not have any appreciable mineralocorticoid effect despite its strong potency as a glucocorticoid.

### Androgen replacement

Unlike glucocorticoid and mineralocorticoid replacement, androgen replacement is nonessential, and not everyone with primary adrenal insufficiency needs it. Men with primary adrenal insufficiency do not require adrenal androgen replacement because they have adequate sources of DHEA, DHEA-S, and testosterone produced by the testes.

In premenopausal women, however, DHEA and DHEA-S are the main circulating androgens and are produced predominantly in the adrenal gland, with only a minor contribution from the ovaries. Physiologic levels are highest in young women and taper off above age 30. Therefore, the ideal candidate for DHEA treatment is a young woman with primary adrenal insufficiency who is experiencing symptoms of low libido, fatigue, and depression, in the absence of a clear alternative cause.<sup>1,41</sup>

The starting dose of DHEA is 25 mg daily, which can be increased to 50 mg daily.<sup>1,42</sup> To assess dose adequacy, blood DHEA-S levels should be checked 3 months after dose changes and then yearly, aiming for a mid-normal DHEA-S level on a day that the DHEA replacement is held. DHEA supplementation should only be continued if there is a significant improvement

in symptoms of depression, energy, or libido. Treatment is done on a 6-month trial basis, and therapy is stopped if there are no clear enduring benefits. Positive effects of treatment may also be self-limited to a few months, even at an appropriate dose. Symptoms of hirsutism, acne, or oily skin can result from DHEA therapy and suggest overreplacement.

### Lifesaving considerations

Lifelong glucocorticoid and mineralocorticoid replacement is essential for all patients with primary adrenal insufficiency. The consequences of missed steroid doses may be as mild as fatigue, or as severe as shock and adrenal crisis. Each year, an alarming 8% of patients with primary adrenal insufficiency experience an adrenal crisis requiring hospital treatment.<sup>43</sup> More than half of adrenal crises develop in the setting of vomiting or diarrhea.<sup>43</sup>

A functional adrenal gland naturally produces higher levels of cortisol in response to stress, but patients with primary adrenal insufficiency cannot mount this same response, as they are dependent on exogenous cortisol. To simulate this adrenal stress response, patients are instructed to double their glucocorticoid dosing ("stress-dose steroids") if they are having intercurrent illnesses such as diarrhea, vomiting, upper respiratory infection, fever, or significant stress. Patients are advised to use stress-dose steroids for 2 to 4 days.<sup>44</sup> If a longer course is necessary, then they are instructed to contact their provider to discuss next steps with the goal of avoiding excessive glucocorticoid exposure. Hospitalized patients with prolonged illness may require longer durations of stress dosing but should be tapered back to their replacement dosage once medically stable.

To reduce avoidable hospitalizations and deaths, it is crucial that patients have ready access to their medications. All patients should keep extra pills available in their car, purse, or luggage, or with nearby friends and family so that they always have medication on hand. An intramuscular glucocorticoid injection kit (such as hydrocortisone 100-mg injection with needle and syringe, which has both glucocorticoid and mineralocorticoid effect) should be prescribed and kept at home if a patient is ever unable to take oral medication. Those who are closest to the patient should be trained to use the parenteral injection kit as needed. If a kit is unavailable, patients should go to an emergency department for prompt steroid treatment. In the event of unconsciousness, medical alert notification (such as a bracelet, necklace, badge, or card) can be lifesaving as it notifies emergency providers to give steroids and fluids.



Typical treatment of suspected adrenal crisis in the emergency department consists of 100 mg of hydrocortisone either intravenously or intramuscularly, followed by a liter of normal saline over 60 minutes.<sup>45</sup> Additional parenteral steroid doses should be given 3 or 4 times per day until the patient is able to restart oral therapy.

Patients with primary adrenal insufficiency and their families must be counseled and periodically reminded of all these interventions to ensure their steroid therapy is adequate and uninterrupted. Patient education is key to avoid overt adrenal insufficiency and adrenal crises. Nonadherence is a significant problem; in a survey

of 81 patients in Europe, 85% reported a degree of nonadherence, and many were dissatisfied with the information they had received from their providers.<sup>38</sup> Only by understanding the rationale that underlies the evaluation and management of primary adrenal insufficiency can providers recognize and treat this disease, increase patient adherence, and lower the risks of adrenal crises and death.

## DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

## REFERENCES

- Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2016; 101(2):364–389. doi:10.1210/jc.2015-1710
- Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. *Lancet* 2014; 383(9935):2152–2167. doi:10.1016/S0140-6736(13)61684-0
- Chabre O, Goichot B, Zenaty D, Bertherat J. Group 1. Epidemiology of primary and secondary adrenal insufficiency: prevalence and incidence, acute adrenal insufficiency, long-term morbidity and mortality. *Ann Endocrinol (Paris)* 2017; 78(6):490–494. doi:10.1016/j.ando.2017.10.010
- Addison T. On the Constitutional and Local Effects of Disease of the Suprarenal Capsules. London: Samuel Highley, 1855. <https://wellcomecollection.org/works/xsmzqpdw>. Accessed August 14, 2024.
- Ngaosuwan K, Johnston DG, Godsland IF, et al. Increased mortality risk in patients with primary and secondary adrenal insufficiency. *J Clin Endocrinol Metab* 2021; 106(7):e2759–e2768. doi:10.1210/clinem/dgab096
- Papierska L, Rabijewski M. Delay in diagnosis of adrenal insufficiency is a frequent cause of adrenal crisis. *Int J Endocrinol* 2013; 2013:482370. doi:10.1155/2013/482370
- Bleicken B, Hahner S, Ventz M, Quinkler M. Delayed diagnosis of adrenal insufficiency is common: a cross-sectional study in 216 patients. *Am J Med Sci* 2010; 339(6):525–531. doi:10.1097/MAJ.0b013e3181db6b7a
- Mountjoy KG. The human melanocyte stimulating hormone receptor has evolved to become “super-sensitive” to melanocortin peptides. *Mol Cell Endocrinol* 1994; 102(1–2):R7–R11. doi:10.1016/0303-7207(94)90113-9
- Hamrahian AH, Fleseriu M; AACE Adrenal Scientific Committee. Evaluation and management of adrenal insufficiency in critically ill patients: disease state review. *Endocr Pract* 2017; 23(6):716–725. doi:10.4158/EP161720.RA
- Dubey A, Boujoukos AJ. Measurements of serum free cortisol in critically ill patients. *Crit Care* 2004; 9(1):E2. doi:10.1186/cc3040
- Le Roux CW, Meeran K, Alaghband-Zadeh J. Is a 0900-h serum cortisol useful prior to a short synacthen test in outpatient assessment? *Ann Clin Biochem* 2002; 39(Pt 2):148–150. doi:10.1258/0004563021901919
- Kumar R, Wassif WS. Adrenal insufficiency. *J Clin Pathol* 2022; 75(7):435–442. doi:10.1136/clinpath-2021-207895
- Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med* 2004; 350(16):1629–1638. doi:10.1056/NEJMoa020266
- Charoensri S, Chailurkit L, Muntham D, Bunnag P. Serum dehydroepiandrosterone sulfate in assessing the integrity of the hypothalamic-pituitary-adrenal axis. *J Clin Transl Endocrinol* 2017; 7:42–46. doi:10.1016/j.jcte.2017.01.001
- Suresh M, Gruber L, Bancos I. The diagnostic accuracy of dehydroepiandrosterone sulfate in diagnosing adrenal insufficiency [abstract]. *J Endocr Soc* 2021; 5(suppl 1):A97–A98. doi:10.1210/jendso/bvab048.195
- Ergin AB, Kennedy AL, Gupta MK, Hamrahian AH. The Cleveland Clinic Manual of Dynamic Endocrine Testing. Switzerland: Springer Cham; 2015.
- Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. *Lancet* 2021; 397(10274):613–629. doi:10.1016/S0140-6736(21)00136-7
- Vita JA, Silverberg SJ, Golland RS, Austin JH, Knowlton AI. Clinical clues to the cause of Addison’s disease. *Am J Med* 1985; 78(3):461–466. doi:10.1016/0002-9343(85)90339-0
- Margaretten W, Nakai H, Landing BH. Septicemic adrenal hemorrhage. *Am J Dis Child* 1963; 105:346–351. doi:10.1001/archpedi.1963.02080040348004
- Xarli VP, Steele AA, Davis PJ, Buescher ES, Rios CN, Garcia-Bunuel R. Adrenal hemorrhage in the adult. *Medicine (Baltimore)* 1978; 57(3):211–221. doi:10.1097/00005792-197805000-00002
- Kovacs KA, Lam YM, Pater JL. Bilateral massive adrenal hemorrhage. Assessment of putative risk factors by the case-control method. *Medicine (Baltimore)* 2001; 80(1):45–53. doi:10.1097/00005792-200101000-00005
- Spartalis E, Drikos I, Ioannidis A, et al. Metastatic carcinomas of the adrenal glands: from diagnosis to treatment. *Anticancer Res* 2019; 39(6):2699–2710. doi:10.21873/anticancer.13395
- Alexandraki KI, Sanpawithayakul K, Grossman A. Adrenal insufficiency. In: Feingold KR, Anawalt B, Blackman MR, et al, eds. *Endotext*. South Dartmouth, MA: MDText.com, Inc.; 2022.
- Porter N, Beynon HL, Randeve HS. Endocrine and reproductive manifestations of sarcoidosis. *QJM* 2003; 96(8):553–561. doi:10.1093/qjmed/hcg103
- Munir S, Quintanilla Rodriguez BS, Waseem M. Addison disease. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2024.
- Raschi E, Fusaroli M, Massari F, et al. The changing face of drug-induced adrenal insufficiency in the Food and Drug Administration adverse event reporting system. *J Clin Endocrinol Metab* 2022; 107(8):e3107–e3114. doi:10.1210/clinem/dgac359
- Veytsman I, Nieman L, Fojo T. Management of endocrine manifestations and the use of mitotane as a chemotherapeutic agent for adrenocortical carcinoma. *J Clin Oncol* 2009; 27(27):4619–4629. doi:10.1200/JCO.2008.17.2775
- Castinetti F, Nieman LK, Reincke M, Newell-Price J. Approach to the patient treated with steroidogenesis inhibitors. *J Clin Endocrinol Metab* 2021; 106(7):2114–2123. doi:10.1210/clinem/dgab122
- Carroll TB, Peppard WJ, Herrmann DJ, et al. Continuous etomidate infusion for the management of severe Cushing syndrome: validation of a standard protocol. *J Endocr Soc* 2018; 3(1):1–12. doi:10.1210/js.2018-00269

30. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncol* 2018; 4(2):173–182. doi:10.1001/jamaoncol.2017.3064
31. Grouthier V, Lebrun-Vignes B, Moey M, et al. Immune checkpoint inhibitor-associated primary adrenal insufficiency: WHO VigiBase report analysis. *Oncologist* 2020; 25(8):696–701. doi:10.1634/theoncologist.2019-0555
32. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy [published correction appears in *N Engl J Med* 2013; 368(6):584]. *N Engl J Med* 2013; 368(2):138–148. doi:10.1056/NEJMoa1209096
33. Degros V, Pons L, Ghulam A, Racadot A. 21-hydroxylase autoantibodies as a marker of adrenal involvement in patients with autoimmune endocrinopathies [In French]. *Ann Biol Clin (Paris)* 1999; 57(6):705–709. PMID:10572219
34. Isidori AM, Venneri MA, Graziadio C, et al. Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial. *Lancet Diabetes Endocrinol* 2018; 6(3):173–185. doi:10.1016/S2213-8587(17)30398-4
35. Johannsson G, Nilsson AG, Bergthorsdottir R, et al. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. *J Clin Endocrinol Metab* 2012; 97(2):473–481. doi:10.1210/jc.2011-1926
36. Kiko N, Kalhan A. Comparison of various glucocorticoid replacement regimens used in chronic adrenal insufficiency: a systematic review. *Dubai Diabetes Endocrinol J* 2020; 26(2):50–68. doi:10.1159/000508321
37. Forss M, Batcheller G, Skrtic S, Johannsson G. Current practice of glucocorticoid replacement therapy and patient-perceived health outcomes in adrenal insufficiency—a worldwide patient survey. *BMC Endocr Disord* 2012; 12:8. doi:10.1186/1472-6823-12-8
38. Chapman SC, Llahana S, Carroll P, Horne R. Glucocorticoid therapy for adrenal insufficiency: nonadherence, concerns and dissatisfaction with information. *Clin Endocrinol (Oxf)* 2016; 84(5):664–671. doi:10.1111/cen.12991
39. Esposito D, Pasquali D, Johannsson G. Primary adrenal insufficiency: managing mineralocorticoid replacement therapy. *J Clin Endocrinol Metab* 2018; 103(2):376–387. doi:10.1210/jc.2017-01928
40. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013; 9(1):30. doi:10.1186/1710-1492-9-30
41. Alkatib AA, Cosma M, Elamin MB, et al. A systematic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. *J Clin Endocrinol Metab* 2009; 94(10):3676–3681. doi:10.1210/jc.2009-0672
42. Arlt W, Callies F, Allolio B. DHEA replacement in women with adrenal insufficiency—pharmacokinetics, bioconversion and clinical effects on well-being, sexuality and cognition. *Endocr Res* 2000; 26(4):505–511. doi:10.3109/07435800009048561
43. White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. *Eur J Endocrinol* 2010; 162(1):115–120. doi:10.1530/EJE-09-0559
44. Rushworth RL, Torpy DJ, Falhammar H. Adrenal crisis. *N Engl J Med* 2019; 381(9):852–861. doi:10.1056/NEJMra1807486
45. Husebye ES, Allolio B, Arlt W, et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. *J Intern Med* 2014; 275(2):104–115. doi:10.1111/joim.12162

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