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Adrenal Insufficiency in Adults
A Review

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IMPORTANCE Adrenal insufficiency is a syndrome of cortisol deficiency and is categorized as primary, secondary, or glucocorticoid induced. Although primary and secondary adrenal insufficiency are rare, affecting less than 279 per 1 million individuals, glucocorticoid-induced adrenal insufficiency is common.

OBSERVATIONS Primary adrenal insufficiency, which involves deficiency of all adrenocortical hormones, is caused by autoimmune destruction, congenital adrenal hyperplasia, pharmacological inhibition (eg, high doses of azole antifungal therapy), infection (eg, tuberculosis, fungal infections), or surgical removal of adrenal cortical tissue. Secondary adrenal insufficiency is caused by disorders affecting the pituitary gland, such as tumors, hemorrhage, inflammatory or infiltrative conditions (eg, hypophysitis, sarcoidosis, hemochromatosis), surgery, radiation therapy, or medications that suppress corticotropin production, such as opioids. Glucocorticoid-induced adrenal insufficiency is caused by administration of supraphysiological doses of glucocorticoids. Patients with adrenal insufficiency typically present with nonspecific symptoms, including fatigue (50%-95%), nausea and vomiting (20%-62%), and anorexia and weight loss (43%-73%). Glucocorticoid-induced adrenal insufficiency should be suspected in patients who have recently tapered or discontinued a supraphysiological dose of glucocorticoids. Early-morning (approximately 8 AM) measurements of serum cortisol, corticotropin, and dehydroepiandrosterone sulfate (DHEAS) are used to diagnose adrenal insufficiency. Primary adrenal insufficiency is typically characterized by low morning cortisol levels (<5 µg/dL), high corticotropin levels, and low DHEAS levels. Patients with secondary and glucocorticoid-induced adrenal insufficiency typically have low or intermediate morning cortisol levels (5-10 µg/dL) and low or low-normal corticotropin and DHEAS levels. Patients with intermediate early-morning cortisol levels should undergo repeat early-morning cortisol testing or corticotropin stimulation testing (measurement of cortisol before and 60 minutes after administration of cosyntropin, 250 µg). Treatment of adrenal insufficiency involves supplemental glucocorticoids (eg, hydrocortisone, 15-25 mg daily, or prednisone, 3-5 mg daily). Mineralocorticoids (eg, fludrocortisone, 0.05-0.3 mg daily) should be added for patients with primary adrenal insufficiency. Adrenal crisis, a syndrome that can cause hypotension and shock, hyponatremia, altered mental status, and death if untreated, can occur in patients with adrenal insufficiency who have inadequate glucocorticoid therapy, acute illness, and physical stress. Therefore, all patients with adrenal insufficiency should be instructed how to increase glucocorticoids during acute illness and prescribed injectable glucocorticoids (eg, hydrocortisone, 100 mg intramuscular injection) to prevent or treat adrenal crisis.

CONCLUSIONS AND RELEVANCE Although primary and secondary adrenal insufficiency are rare, glucocorticoid-induced adrenal insufficiency is a common condition. Diagnosis of adrenal insufficiency involves early-morning measurement of cortisol, corticotropin, and DHEAS. All patients with adrenal insufficiency should be treated with glucocorticoids and instructed how to prevent and treat adrenal crisis.

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Primary adrenal insufficiency, which is characterized by deficient production of cortisol and aldosterone by the adrenal gland, is most commonly caused by autoimmune adrenalitis. Often called Addison disease, primary adrenal insufficiency is rare, with global prevalence estimates ranging from 4 to 221 cases per 1 million.[1-5] Secondary adrenal insufficiency, which is characterized by decreased pituitary gland production of corticotropin (also known as adrenocorticotropic hormone [ACTH]), may be caused by pituitary gland tumors, hemorrhage, inflammation (such as hypophysitis and sarcoidosis), surgery, or radiation therapy, or by medications that suppress corticotropin production, such as opioids. Secondary adrenal insufficiency occurs globally in 140 to 279 per 1 million individuals. Glucocorticoid-induced adrenal insufficiency, sometimes also known as tertiary adrenal insufficiency, is caused by suppression of corticotropin-releasing hormone (CRH) from the hypothalamus, which prevents corticotropin release from the pituitary. While the incidence of glucocorticoid-induced adrenal insufficiency is unknown, it is the most common form of adrenal insufficiency globally, as up to 1% to 3% of the adult population is prescribed glucocorticoid therapy.[6] Most patients with primary adrenal insufficiency and secondary adrenal insufficiency have months to years of nonspecific symptoms (such as fatigue, nausea, abdominal pain, and anorexia) before diagnosis,[7-12] and up to 50% experience an adrenal crisis,[11,13] a life-threatening state of cortisol deficiency that can lead to hypovolemic or distributive shock that is resistant to vasopressor support, severe hyponatremia with altered mental status, and death.

This Review summarizes the pathophysiology of adrenal insufficiency and approaches to diagnosis, treatment, and prevention of adrenal crisis. The **Box** provides some common questions and answers about adrenal insufficiency.

Box. Commonly Asked Questions About Adrenal Insufficiency

What Is Adrenal Insufficiency?

Adrenal insufficiency is a syndrome of cortisol deficiency that often presents with nonspecific symptoms such as fatigue (50%-95%), nausea and vomiting (20%-62%), and anorexia and weight loss (43%-73%). The most severe presentation of adrenal insufficiency is adrenal crisis, a life-threatening syndrome caused by relative cortisol insufficiency that can lead to altered mental status, shock, and death if left untreated.

How Is Adrenal Insufficiency Diagnosed?

An early-morning serum cortisol level of less than 5 µg/dL is considered highly probable for adrenal insufficiency, and morning cortisol concentrations greater than 10 µg/dL indicate a very low likelihood of adrenal insufficiency. Low or low-normal dehydroepiandrosterone sulfate (DHEAS) levels further support the diagnosis of adrenal insufficiency. Early-morning measurement of corticotropin can help determine if adrenal insufficiency is primary or secondary.

How Is Adrenal Insufficiency Treated?

Patients with adrenal insufficiency require treatment with physiological doses of glucocorticoid (eg, hydrocortisone, 15-25 mg daily, or prednisone or prednisolone, 3-5 mg daily). Primary adrenal insufficiency also requires mineralocorticoid therapy (eg, fludrocortisone, 0.05-0.3 mg daily). All patients with adrenal insufficiency should be instructed about the need to increase glucocorticoid dosing during illness or stress and taught how to use injectable glucocorticoids to prevent adrenal crisis.

Methods

A PubMed search was performed for English-language articles of randomized clinical trials, systematic reviews, meta-analyses, and observational studies related to the diagnosis and treatment of adrenal insufficiency in adults aged 18 years or older published between January 1, 1994, and March 1, 2025. Search terms used included *adrenal insufficiency* OR *Addison's disease* OR *adrenal crisis*. Of the 405 studies identified, 23 were considered pertinent for this Review. In addition, the most recent clinical practice guidelines on adrenal insufficiency published by the Endocrine Society,[14] the Society of Critical Care Medicine,[15] jointly by the Endocrine Society and the European Society of Endocrinology,[6] and the National Institute for Health and Care Excellence[16] were reviewed to identify 48 additional references. In total, we included 4 randomized clinical trials, 23 cohort studies, 21 cross-sectional studies, 7 systematic reviews and meta-analyses, 13 clinical practice guidelines and narrative reviews, 2 case series, and 1 nonclinical study.

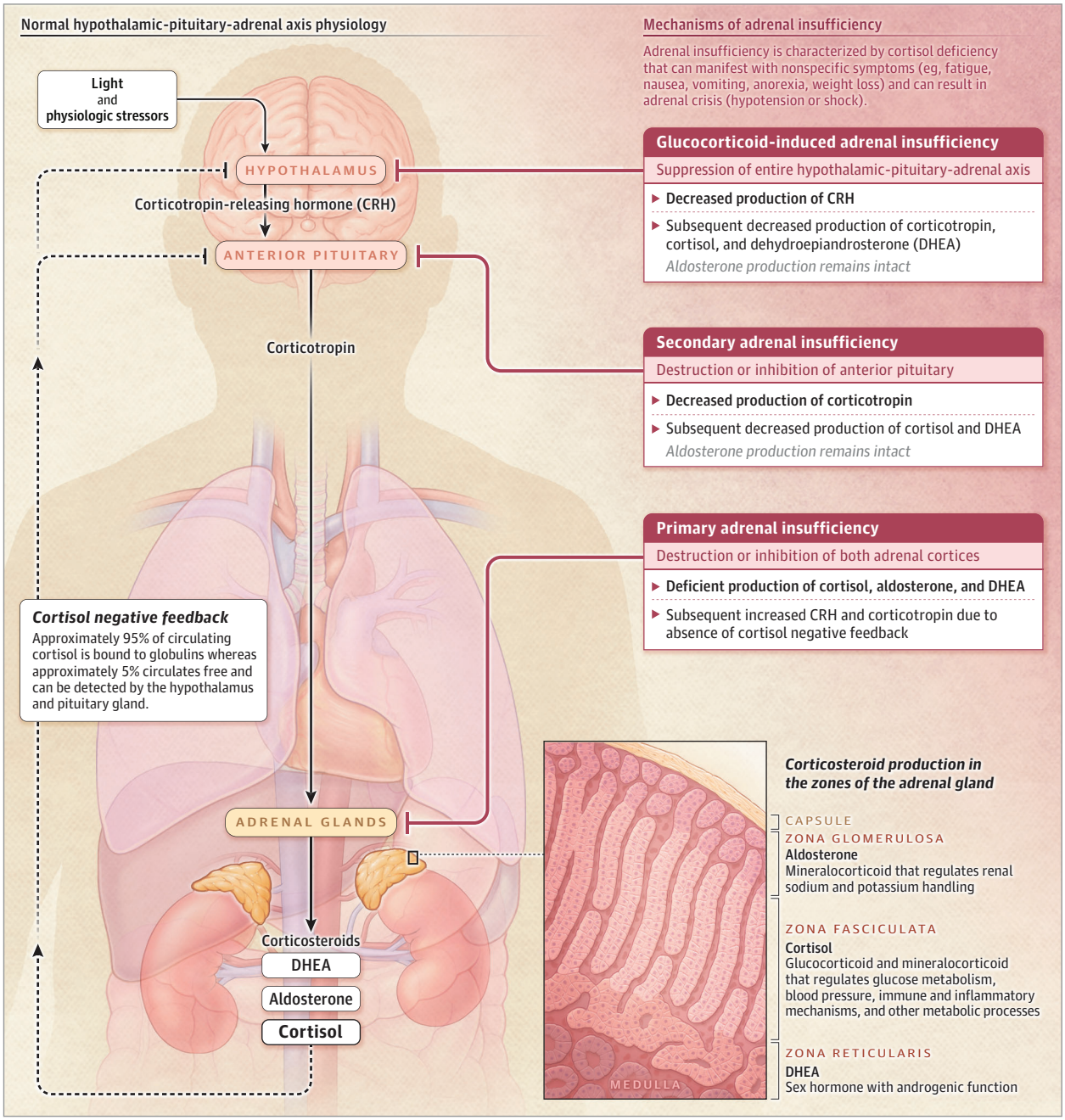
Pathophysiology

Adrenocortical production of cortisol is regulated by the hypothalamic-pituitary-adrenal axis (**Figure 1**). The hypothalamus produces CRH in response to light (typically exhibiting diurnal variation) and stressors, such as fever, hypoglycemia, hypotension, pain, and/or acute illness. CRH induces formation and release of corticotropin from the anterior pituitary, which stimulates the adrenal cortex to produce circulating glucocorticoids, mineralocorticoids, and androgens. While the production of aldosterone is regulated by corticotropin, it is also independently regulated by angiotensin II and extracellular potassium. Therefore, corticotropin deficiency does not induce aldosterone deficiency. Corticotropin has structural similarities to melanocyte-stimulating hormone, and elevated corticotropin levels can directly stimulate production of melanin by melanocytes, resulting in hyperpigmentation.

Once cortisol is released into the circulation, 95% is bound to cortisol-binding globulin or albumin, and approximately 5% circulates as free cortisol, which binds to intracellular glucocorticoid receptors to induce gluconeogenesis, glycogenolysis, lipolysis, and proteolysis and maintain vascular tone. Free cortisol detected by the hypothalamus and pituitary gland results in decreased production of CRH and corticotropin, which decreases cortisol synthesis, a process termed *negative feedback* (Figure 1). Cortisol is also a mineralocorticoid, although most of its mineralocorticoid effect in the kidney is inactivated by 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to cortisone.

Primary adrenal insufficiency results in deficiency of all adrenocortical hormones, including low levels of cortisol, aldosterone, and the adrenal androgens dehydroepiandrosterone (DHEA) and androstenedione, as well as marked elevations in corticotropin as a result of decreased negative feedback (Figure 1).

Figure 1. Pathophysiology of Adrenal Insufficiency



CRH is secreted by the hypothalamus in response to light and physiologic stressors. CRH stimulates corticotropin (also known as adrenocorticotropic hormone [ACTH]) production and secretion from the anterior pituitary gland, which in turn exerts endocrine effects on the adrenal cortex. Corticotropin stimulates production of all adrenal steroidogenesis, including cortisol from the zona fasciculata, aldosterone from the zona glomerulosa, and DHEA from the zona reticularis. Circulating free cortisol exerts negative feedback on the hypothalamus and anterior pituitary to downregulate its own production. Primary adrenal insufficiency is the consequence of the destruction or inhibition of both adrenal cortices such that the production of adrenocortical steroids is diminished or deficient. The absence of negative feedback by cortisol results in upregulation of CRH and corticotropin production. Secondary adrenal insufficiency is the consequence of destruction or inhibition of the anterior pituitary gland such that corticotropin production is deficient. The absence of corticotropin results in cortisol and DHEA deficiency; however, aldosterone production remains relatively normal due to alternative stimulation by the renin-angiotensin system and extracellular potassium. Glucocorticoid-induced adrenal insufficiency is sometimes referred to as secondary and/or tertiary adrenal insufficiency because it is the consequence of exogenous glucocorticoids inducing suppression of the entire hypothalamic-pituitary-adrenal axis. Inhibition of CRH results in deficiency of corticotropin and, consequently, cortisol production.

Secondary adrenal insufficiency occurs due to deficient pituitary production of corticotropin. Although cortisol and adrenal androgen production are entirely dependent on the presence of corticotropin, aldosterone production by the adrenal gland remains

Table 1. Causes of Adrenal Insufficiency in Adults

Primary adrenal insufficiency	Secondary adrenal insufficiency	Glucocorticoid-induced adrenal insufficiency
Autoimmune (67%-90%) • Isolated • Polyglandular syndrome type 1 • Polyglandular syndrome type 2	Tumors • Pituitary adenoma • Pituitary carcinoma • Craniopharyngioma • Primary central nervous system tumor • Metastatic lesions to the pituitary or sella	Exogenous glucocorticoids • Oral • Intravenous • Inhaled • Intranasal • Intra-articular • Topical
Congenital adrenal hyperplasia (5.4%-10%) • 21-Hydroxylase deficiency • 11β-Hydroxylase deficiency • 3β-Hydroxylase deficiency • 17α-Hydroxylase deficiency • Other	Trauma/injury/hemorrhage • Pituitary trauma • Central nervous system hemorrhage or trauma • Sheehan syndrome • Radiation	
Infectious (<5%) • Tuberculosis • Fungal (histoplasmosis, cryptococcosis, coccidiomycosis, blastomycosis) • Viral (cytomegalovirus, HIV)	Hypophysitis • Primary autoimmune hypophysitis • Drug-induced hypophysitis (ipilimumab, nivolumab, pembrolizumab, atezolizumab)	
Infiltrative (<5%) • Metastases from extra-adrenal malignancy • Adrenal lymphoma • Sarcoidosis • Amyloidosis	Infiltrative • Langerhans cell histiocytosis • Amyloidosis • Hemochromatosis • Sarcoidosis	
Medications (<5%) • Antifungals (ketoconazole, levoketoconazole, itraconazole, fluconazole, posaconazole) • Mitotane • Abiraterone acetate • Metyrapone • Osilodrostat • Mifepristone • Immunotherapies (ipilimumab, nivolumab, pembrolizumab) • Heparin	Medications • Opioids • Megesterol acetate	
Other • Hemorrhage • Surgical resection	Other • Hemorrhage • Surgical resection	

normal because it is regulated by angiotensin II and potassium (Figure 1 and **Table 1**). Prolonged corticotropin deficiency results in atrophy of the adrenal cortex and decreased ability to produce cortisol.

Use of exogenous glucocorticoids in supraphysiological doses (eg, prednisone, >5 mg daily) induces negative feedback to suppress CRH and corticotropin production, resulting in decreased endogenous adrenal production of cortisol and androgens (Figure 1). With prolonged exposure to supraphysiological doses of glucocorticoids, atrophy occurs in both the pituitary corticotrophs that produce corticotropin and the adrenal cortex. In addition, opioids such as morphine, oxycodone, and fentanyl can suppress hypothalamic CRH and induce adrenal insufficiency, although how much each opioid analogue induces hypothalamic-pituitary-adrenal suppression is not predictable or consistent.[17-19]

Epidemiology

Primary adrenal insufficiency is rare, with prevalence estimates in Europe of 117 cases per 1 million (ascertained in Italy in 1996),[1] 144 cases per 1 million (ascertained in Norway between 1993 and 2007),[2] and 221 cases per 1 million (ascertained in Iceland in 2012),[3] with slightly higher prevalence among women compared with men.[1] In other areas of the world, such as South Korea, prevalence estimates of primary adrenal insufficiency are lower (4 cases per million, ascertained between 2000 and 2014).[4] The most common causes of primary adrenal insufficiency are autoimmune adrenalitis (90% of all cases in North American and Europe) and inherited disorders of adrenal steroidogenesis, such as congenital adrenal hyperplasia due to 21-hydroxylase deficiency (approximately 1 in 15 000 live births).[20] However, infectious adrenalitis may be the leading cause of primary adrenal insufficiency in areas of the world with high rates of tuberculous and/or HIV infection (Table 1).[21] Primary adrenal insufficiency can occur at any age; however, most cases occur between ages 20 and 50 years.[22] Accurate prevalence statistics for the causes of secondary adrenal insufficiency are not available, but the best available estimates indicate that it is rare, ranging from 140 to 279 per 1 million individuals (Table 1).[23-25]

Use of immune checkpoint inhibitor therapies can cause irreversible primary or secondary adrenal insufficiency. Most affected individuals have secondary adrenal insufficiency from hypophysitis, with incidence rates of 3.2% for ipilimumab, 0.4% for nivolumab or pembrolizumab, less than 0.1% for atezolizumab, and 6.4% for the combination of nivolumab plus ipilimumab.[26] Immune checkpoint inhibitor–induced adrenal insufficiency typically occurs 2 months to 8 months after initiation of treatment.[27,28] Approximately 5% of patients with immune checkpoint inhibitor–induced adrenal insufficiency have primary adrenal insufficiency due to autoimmune adrenalitis.[29,30]

Although the exact incidence of glucocorticoid-induced adrenal insufficiency is unknown, it is the most common form of adrenal

Table 2. Diagnosis and Treatment of Adrenal Insufficiency

	Primary adrenal insufficiency	Secondary adrenal insufficiency	Glucocorticoid-induced adrenal insufficiency
Ascertaining the pretest probability of adrenal insufficiency			
Symptoms suggestive of adrenal insufficiency	• Fatigue (95%) • Nausea, vomiting, abdominal discomfort (62%) • Anorexia and weight loss (67%-73%) • Hyperpigmentation (74%) • Orthostatic hypotension (68%) • Muscle and/or joint pain (40%) • Salt craving (12%-19%)	• Fatigue (50%-76%) • Nausea, vomiting, abdominal discomfort (20%-48%) • Anorexia and weight loss (29%-43%)	• With supraphysiological glucocorticoid use (about 10% to 100%): weight gain, muscle mass loss, weakness • When reducing glucocorticoids to below physiological doses (about 10% to 100%): fatigue, nausea, abdominal discomfort, arthralgias, myalgias
General laboratory studies			
Basic metabolic panel	Hyponatremia or hyperkalemia (35%)	Hyponatremia (4%-10%)	
Complete blood cell count	• Anemia (13%) • Eosinophilia (rare) • Lymphocytosis	• Eosinophilia (rare) • Lymphocytosis	• Eosinopenia • Lymphopenia
Diagnostic tests for adrenal insufficiency			
Testing in the morning	• Low cortisol • High corticotropin • Low or low-normal DHEAS • Low aldosterone • High renin	• Low cortisol • Low or low-normal corticotropin • Low or low-normal DHEAS	• Low cortisol • Low or low-normal corticotropin • Low or low-normal DHEAS
Dynamic testing (if needed)	Cosyntropin stimulation test (not needed if baseline cortisol is low and corticotropin is high)[a]	• Cosyntropin stimulation test[a] • Overnight metyrapone test • Insulin tolerance test	Usually not necessary
Ascertaining the subtype of adrenal insufficiency			
Laboratory	• 21-Hydroxylase antibodies • Very long-chain fatty acids • 17-Hydroxyprogesterone	Consider tests for pituitary target gland deficiencies (eg, thyrotropin, thyroxine, prolactin, growth hormone, insulin-like growth factor 1, follicle-stimulating hormone, luteinizing hormone)	Not needed
Imaging	Computed tomography of the abdomen (needed only if etiology not established by laboratory assessments)	Pituitary magnetic resonance imaging	Not needed
Treatment and management			
Glucocorticoid therapy	Hydrocortisone, 15-25 mg daily (eg, 15 mg on waking, 5 mg 6-8 hours later), *or* prednisone, 3-5 mg each morning	Hydrocortisone, 15-25 mg daily (eg, 15 mg on waking, 5 mg 6-8 hours later), *or* prednisone, 3-5 mg each morning	Hydrocortisone, 15-25 mg daily (eg, 15 mg on waking, 5 mg 6-8 hours later), *or* prednisone, 3-5 mg each morning
Mineralocorticoid therapy	Fludrocortisone, 0.05-0.3 mg daily (usual daily dose, 0.1 mg)	Not needed	Not needed
Education	Reasoning for the dosing/timing of glucocorticoids, approach to special situations, management during sickness/stress dosing, medical alert system (eg, necklace, bracelet), how to use injectable glucocorticoids	Reasoning for the dosing/timing of glucocorticoids, approach to special situations, management during sickness/stress dosing, medical alert system (eg, necklace, bracelet), how to use injectable glucocorticoids	Reasoning for the dosing/timing of glucocorticoids, approach to special situations, management during sickness/stress dosing, medical alert system (eg, necklace, bracelet), how to use injectable glucocorticoids
Monitoring	• Symptoms, circumstances around stress dosing • Yearly monitoring for autoimmune conditions • Physical examination (features of glucocorticoid and mineralocorticoid deficiency/excess) • Mineralocorticoid replacement: electrolytes, renin plasma activity, blood pressure	• Symptoms, circumstances around stress dosing • Physical examination (features of glucocorticoid deficiency/excess)	• Symptoms, circumstances around stress dosing • Physical examination (features of glucocorticoid deficiency/excess) • Monitoring for recovery of adrenal function (morning cortisol measurement after withholding glucocorticoids for 24 hours)

Abbreviation: DHEAS, dehydroepiandrosterone sulfate.

[a] Measure serum cortisol before and 60 minutes after administration of 250 µg of intravenous or intramuscular cosyntropin.

insufficiency. A daily dose of 5 mg or greater of prednisone (or its equivalent) for 3 to 4 weeks or longer can induce adrenal insufficiency.[6]

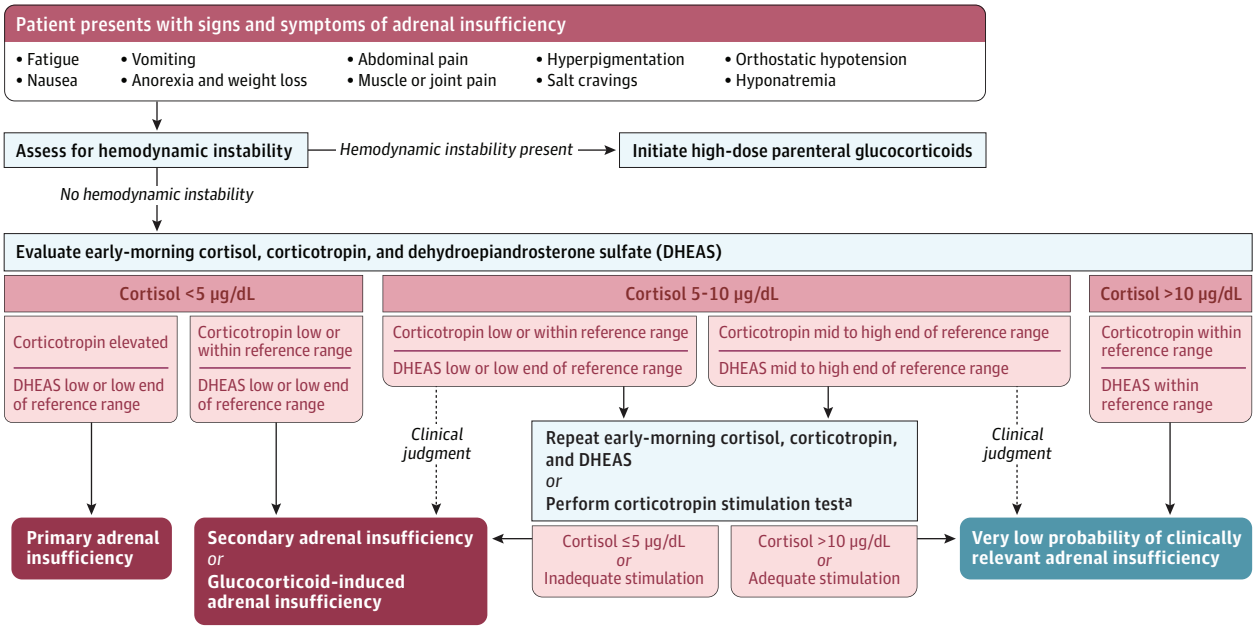
Clinical Presentation and Causes

Patients with adrenal insufficiency commonly experience fatigue (50%-95%); nausea, vomiting, and abdominal pain (20%-62%); muscle or joint paint (40%-53%); and anorexia and weight loss (43%-73%) (**Table 2**).[2,7-11]

A cross-sectional study of 213 patients with primary or secondary adrenal insufficiency showed that 20% reported such nonspecific symptoms for more than 5 years prior to diagnosis.[7] In addition, less than 30% of women and less than 50% of men in this study were diagnosed with adrenal insufficiency within the first 6 months of symptom onset.[7] In another cross-sectional study of 696 patients, median symptom duration was 1 year prior to initiation of therapy.[12]

Most patients with primary adrenal insufficiency develop hyperpigmentation (74%).[2] They may also report salt cravings (12%-19%) and have orthostatic hypotension (68%) due to concomitant

Figure 2. Suggested Approach to Diagnosing Adrenal Insufficiency



When adrenal insufficiency is suspected in a critically ill or hemodynamically unstable patient, high-dose parenteral glucocorticoids should be administered without delay. If random serum cortisol, corticotropin, and DHEAS measurements can be obtained before administration of glucocorticoids, they may have diagnostic value; however, laboratory testing should not delay treatment. For stable, ambulatory patients with suspected adrenal insufficiency, a morning (approximately 8 AM) blood test to measure serum cortisol, corticotropin, and DHEAS should be performed. In patients who sleep during the day and work at night, testing should be performed in the morning after normalization of the circadian rhythm (for example, while on vacation, on weekends, or during long stretches of return to normal sleep-wake cycles), or use dynamic testing such as corticotropin stimulation tests.

[a]Measurement of cortisol before and 60 minutes after intravenous or intramuscular administration of 250 µg of cosyntropin; cortisol levels >18 µg/dL after cosyntropin administration indicate adequate stimulation.

mineralocorticoid deficiency, which may cause hyperkalemia and hyponatremia (35%).[2] Patients with secondary adrenal insufficiency may present with hyponatremia (4%-10%).[31]

Patients with glucocorticoid-induced adrenal insufficiency may initially develop signs and symptoms of Cushing syndrome, such as weight gain, central obesity, sarcopenia with proximal muscle weakness, skin fragility, and easy bruising[6] due to treatment with supraphysiological doses of glucocorticoids. These patients may then develop symptoms of adrenal insufficiency when their daily glucocorticoid dose is reduced below physiological supplemental doses, typically defined as 15 to 25 mg daily of hydrocortisone or 3 to 5 mg daily of prednisone or prednisolone.

Adrenal Crisis

Although there is no universally accepted definition of *adrenal crisis*, this term is typically used to describe cortisol insufficiency that causes hypotension, hypovolemic or distributive shock that is resistant to vasopressor support, and severe hyponatremia with altered mental status and/or somnolence or altered consciousness. Adrenal crisis has a mortality rate of 0.5%. While adrenal crisis is reported by 5% to 8% of patients with all types of adrenal insufficiency,[32] up to 50% of patients with primary adrenal insufficiency experience at least 1 adrenal crisis prior to diagnosis of adrenal insufficiency.[11,13] Adrenal crisis is the cause of death in 15% of persons with Addison disease.[33]

Assessment and Diagnosis

In the absence of a serious illness, early-morning testing of cortisol, corticotropin, and dehydroepiandrosterone sulfate (DHEAS) usually provides sufficient evidence to diagnose adrenal insufficiency (**Figure 2**). The evaluation of morning cortisol concentrations assumes that a patient follows a pattern of sleeping at night and being awake during the day such that peak cortisol levels are expected in the morning and trough levels close to midnight.

Cortisol

Cortisol and corticotropin production follow a circadian rhythm. Peak levels occur in the early morning, just before waking, according to an individual's sleep cycle, followed by a gradual decline throughout the day, and nadir overnight when sleeping.[34,35] Early-morning evaluation of serum cortisol (at approximately 8 AM) is the recommended initial test to evaluate for adrenal insufficiency[6,14]; however, its interpretation may be limited by variability of cortisol production as a function of each individual's circadian rhythm and the time of the blood draw.[36] In a retrospective cohort of 804 patients being evaluated for adrenal insufficiency (46.7% prevalence of adrenal insufficiency), an early-morning cortisol level greater than 16 µg/dL had a negative predictive value for the diagnosis of adrenal insufficiency of 98.7%; a basal cortisol level of less than 3.6 µg/dL had a positive predictive value of 93.2% to diagnose adrenal insufficiency.[37] In a retrospective study of 1135 patients being

evaluated for adrenal insufficiency, a basal cortisol level of 10 µg/dL or greater excluded adrenal insufficiency in 98.8% of patients.[38] Among 416 patients in a retrospective study, a cortisol value of less than 3.0 µg/dL was 99.7% specific for adrenal insufficiency while a cortisol value greater than 12.7 µg/dL was 98.9% sensitive; values between 3 µg/dL and 12.7 µg/dL were considered intermediate.[39]

Guidelines from the European Society of Endocrinology and the Endocrine Society state that an early-morning cortisol measurement greater than 10 µg/dL very likely indicates relatively normal hypothalamic-pituitary-adrenal axis function and therefore has a very low probability of clinically relevant adrenal insufficiency.[6] Conversely, an early-morning serum cortisol level of less than 5 µg/dL in patients with clinical features concerning for adrenal insufficiency is considered highly probable of adrenal insufficiency.[6] The use of early-morning salivary free cortisol as a method to test for adrenal insufficiency with samples collected at home has recently been investigated, and a salivary free cortisol level greater than 180 ng/dL (5 nmol/L) excluded adrenal insufficiency with a sensitivity of 95%.[40]

Corticotropin

When combined with an early-morning cortisol measurement, corticotropin concentrations help determine the type of adrenal insufficiency. Nearly all patients with primary adrenal insufficiency have elevated plasma corticotropin (usually >100 pg/mL; reference range, 15-65 pg/mL). In contrast, patients with secondary and glucocorticoid-induced adrenal insufficiency have corticotropin concentrations that are below or at the lower end of the reference range (usually <20 pg/mL) (Figure 2 and Table 2).[14,22]

Dehydroepiandrosterone Sulfate

In primary adrenal insufficiency, all adrenocortical steroid levels are low (including DHEA and its stable sulfated metabolite, DHEAS). In secondary and glucocorticoid-induced adrenal insufficiency, the insufficiency or deficiency of corticotropin results in low or low-normal levels of DHEAS.[41] Because DHEAS circulates in high concentrations (3-6 orders of magnitude higher than cortisol) and has a long half-life (7-10 hours), DHEAS serves as an accurate predictive marker of hypothalamic-pituitary-adrenal axis impairment. In a study of 1135 patients, DHEAS concentrations demonstrated good diagnostic accuracy for adrenal insufficiency, especially in patients without a history of glucocorticoid use (area under the curve of 0.83); when cortisol concentrations were in the indeterminate range of 5 to 9.9 µg/dL and when DHEAS was greater than 60 µg/dL, adrenal insufficiency was excluded in 98.7% of patients.[38]

Adrenal Antibodies

More than 90% of patients with primary adrenal insufficiency have circulating 21-hydroxylase antibodies, which confirms the diagnosis of autoimmune adrenalitis.[42] The absence of these antibodies does not exclude primary adrenal insufficiency but should lead to evaluation for other, nonautoimmune causes of primary adrenal insufficiency (Table 1).

Dynamic Testing

Dynamic assessment of adrenal function may be useful when early-morning testing is equivocal (eg, morning serum cortisol level of 5-10 µg/dL) in patients considered likely to have adrenal insufficiency. Dynamic testing with the corticotropin stimulation test evaluates cortisol before and 60 minutes after intravenous (or intramuscular) administration of 250 µg of cosyntropin (corticotropin[1-24]). The expected peak cortisol level following administration of cosyntropin is 18 µg/dL or greater at 60 minutes.[43] A systematic review and meta-analysis that included 28 studies with 1437 patients who had secondary adrenal insufficiency reported that a cortisol level of less than 18 to 20 µg/dL at 30 or 60 minutes after administration of cosyntropin, 250 µg, had a sensitivity of 64% and a specificity of 93% for diagnosis of adrenal insufficiency.[44] Thus, some patients with secondary adrenal insufficiency may have a normal corticotropin stimulation test finding, especially those in whom corticotropin deficiency has been of short duration (days to weeks).

Other dynamic diagnostic tests include the overnight metyrapone test, insulin-induced hypoglycemia, and glucagon stimulation test, which are reserved for patients considered likely to have secondary adrenal insufficiency but who had a normal or equivocal cosyntropin stimulation test finding. Insulin-induced hypoglycemia and glucagon stimulation tests are resource intensive and may not be readily available outside of specialized centers. The overnight metyrapone test has high accuracy for identifying secondary adrenal insufficiency,[45] but metyrapone is typically not readily available, so this test is rarely used.

Treatment

Management of adrenal insufficiency involves determining the appropriate physiological supplemental dose of glucocorticoid (and mineralocorticoid, if applicable), patient education about glucocorticoid dosing, and management of glucocorticoid therapy during illness or stress to prevent adrenal crisis (Table 2).

Glucocorticoid Therapy

Physiological glucocorticoid therapy should be initiated in all patients with adrenal insufficiency. Physiological dosing refers to therapy given to mimic the amount and timing of the body's natural production of cortisol.

Hydrocortisone, which is bioidentical to cortisol, is a short-acting oral glucocorticoid (peak concentrations 2-3 hours after ingestion), and a dose of approximately 15 to 25 mg daily (approximately 12 mg/m^2 daily) is generally sufficient for most adult patients with adrenal insufficiency; the daily dose can be divided into 2 doses, with the first and larger dose taken on waking (eg, two-thirds of the daily dose taken on waking) and the second and smaller dose no later than 6 hours prior to sleep (eg, one-third of the daily dose taken in the early afternoon).[12,21] Prednisone or prednisolone is a longer-acting oral glucocorticoid that is commonly used and can be administered once daily, typically at doses of 3 to 5 mg.[6] Because there is no clear evidence indicating improved outcomes with one glucocorticoid compared with the others, the decision to use supplemental hydrocortisone, prednisone, or prednisolone is based on patient and clinician preferences. Other glucocorticoids (such as methylprednisolone or dexamethasone) are not recommended for daily treatment of adrenal insufficiency given their long half-life (which does not replicate the normal circadian pattern of cortisol), high potency, and risk of inducing Cushing syndrome.

After treatment initiation, the steroid dose must be individualized because serum cortisol and plasma corticotropin are not helpful

Table 3. Guidelines for Prescribing Stress-Dose Glucocorticoid Treatment for Adults With Adrenal Insufficiency[a]

	Suggested regimen
Minor stress	
Illness requiring bed rest; illness with fever (out of hospital); illness requiring treatment with antibiotics (out of hospital); significant emotional stress (eg, bereavement, major psychiatric episode)	• Hydrocortisone: increase to 40-mg total daily dose, to be given in 3 divided doses (eg, 20 mg on rising, 10 mg at midday, and 10 mg in mid-afternoon); continue for 2-5 days until well (or for duration of antibiotic treatment) • Prednisone: increase to 10-mg total daily dose, to be given in 1 or 2 divided doses; continue for 2-5 days until well (or for duration of antibiotic treatment)
Minor surgery, including any procedure requiring local anesthesia	• Hydrocortisone: increase to 40-mg total daily dose, to be given in 3 divided doses (eg, 20 mg 1 hour prior to procedure, 10 mg 6 hours after procedure, and 10 mg after a further 6 hours); continue increased dose in patients who remain unwell after procedure until clinically stable • Prednisone: increase to 10-mg total daily dose, to be given 1 hour prior to procedure; continue increased dose in patients who remain unwell after procedure until clinically stable
Bowel procedures not carried out under general anesthesia	Continue usual or double glucocorticoid dose on day of procedure; give an equivalent intravenous dose if prolonged nil by mouth
Major stress/adrenal crisis	
Severe or critical illness, for example: persistent vomiting or diarrhea from gastrointestinal illness; infection requiring hospital admission or intravenous antibiotics (eg, sepsis); acute trauma, pain, or significant blood loss; unexplained hemodynamic compromise, hypotension, shock, or critical illness	• For patients with persistent vomiting or diarrhea: hydrocortisone, 100-mg intramuscular injection immediately; patients should be seen at a health care facility for intravenous fluids • For patients requiring hospital admission: hydrocortisone, 100-mg intravenous bolus or intramuscular injection immediately, followed by hydrocortisone, 50-mg intravenous boluses every 6 hours, or, alternatively, a continuous infusion of hydrocortisone, 200 mg, over 24 hours; the duration and dose of the glucocorticoid regimen thereafter must be individualized based on the stressor type and patient's clinical status
Surgery or any procedure requiring general or regional anesthesia with anticipated short recovery time and no nil by mouth	• Intraoperative regimen: hydrocortisone, 100-mg intravenous bolus at induction, followed by hydrocortisone, 50-mg intravenous boluses every 6 hours, or, alternatively, a continuous infusion of hydrocortisone, 200 mg, over 24 hours • Postoperative regimen: resume oral glucocorticoids at an increased dose for 48 hours and then resume presurgical dose; in case of postoperative complications (eg, significant pain, infections), maintain an increased oral dose or give stress-dose glucocorticoids intravenous as clinically appropriate
Surgery (including cesarean delivery) or any procedure requiring general or regional anesthesia with nil by mouth or expected long recovery time	• Intraoperative regimen: hydrocortisone, 100-mg intravenous bolus at induction, followed by hydrocortisone, 50-mg intravenous boluses every 6 hours, or, alternatively, a continuous infusion of hydrocortisone, 200 mg, over 24 hours • Postoperative regimen: if the postoperative period is uncomplicated and once the patient can eat, resume oral glucocorticoids at 2-3 times the basal dose, then transition to presurgical dose; in case of postoperative complications (eg, significant pain, infections), maintain an increased oral dose or give stress-dose glucocorticoids intravenous as clinically appropriate
Labor and vaginal delivery	Hydrocortisone, 100-mg intravenous bolus at onset of labor, followed by hydrocortisone, 50-mg intravenous boluses every 6 hours, or, alternatively, a continuous infusion of hydrocortisone, 200 mg over 24 hours

[a] Table adapted with permission from the European Society of Endocrinology and Endocrine Society joint clinical guideline.[6]

to guide treatment due to their variability throughout the day. The daily dose and frequency of administration should be subsequently determined by a patient's general well-being and functionality, with the goal of using the lowest steroid dose to achieve subjective well-being.

Steroid Dosing During Acute Illness or Stress

To accommodate the increased physiological need for glucocorticoids during stress, all patients with adrenal insufficiency should receive higher doses of glucocorticoids during stressors, such as infections and surgeries requiring general anesthesia. Increased steroid dosing may also be considered for patients during times of intense mental or emotional stress, such as bereavement and intense grief (**Table 3**). Specific glucocorticoid medications and dosing recommendations for patients with adrenal insufficiency and in acute illness or stress are outlined in Table 3. These recommendations should also be applied for patients considered at high likelihood of having adrenal insufficiency but before adrenal insufficiency is confirmed.[6,46]

Hemodynamically unstable or critically ill patients known or suspected to have adrenal insufficiency should receive urgent treatment with parenteral high-dose glucocorticoids (ie, 1 intravenous administration of hydrocortisone, 100 mg) (Figure 2).

Adrenal Crisis

Adrenal crisis is a life-threatening emergency and should be treated promptly with high-dose intravenous glucocorticoid therapy and other supportive care such as intravenous fluids and vasopressors (doses and duration are dependent on the clinical situation) (Table 3).[6]

Mineralocorticoid Therapy

Although patients with secondary and glucocorticoid-induced adrenal insufficiency do not develop mineralocorticoid deficiency, most patients with primary adrenal insufficiency have mineralocorticoid deficiency that requires replacement with fludrocortisone. The usual starting dose of fludrocortisone is 0.1 mg daily, with down- or up-titration to 0.05 mg and 0.3 mg daily.[47] Monitoring of mineralocorticoid replacement therapy includes clinical assessment of energy level and general well-being, physical examination for volume depletion or peripheral edema, and laboratory measurements to assess sodium and potassium.[47,48] Signs of mineralocorticoid underreplacement include salt craving, orthostatic hypotension, elevated serum potassium, hyponatremia, and elevated renin. Signs of mineralocorticoid overreplacement include edema, hypertension, hypokalemia, and suppressed renin. Although some studies have shown that plasma renin levels can

guide fludrocortisone dosing, others have not[48-51]; therefore, routine monitoring of plasma renin in patients with primary adrenal insufficiency is not recommended.

Androgen Therapy

Several studies have shown that DHEA replacement in both women and men with primary adrenal insufficiency and secondary adrenal insufficiency may improve quality of life, mood, and sex drive.[52-55] However, a systematic review and meta-analysis that included 10 randomized clinical trials with 264 patients reported only a small overall clinical benefit (for general quality of life, a pooled standardized mean difference of 0.21 [95% CI, 0.08-0.33]); for depression, a pooled standardized mean difference of 0.23 [95% CI, 0.04-0.42]).[56] Clinical practice guidelines recommend DHEA replacement therapy in women with adrenal insufficiency who have low libido, fatigue, and symptoms of depression.[14] The recommended starting dose is typically 25 mg daily, with a goal of titrating the dose to a mid-normal serum DHEAS concentration.[14] If no symptomatic benefit is seen after 6 months of therapy, DHEA can be discontinued. Signs of androgen overreplacement include acne and hirsutism.

Management Considerations in Patients With Glucocorticoid-Induced Adrenal Insufficiency

Although glucocorticoid-induced adrenal insufficiency is typically due to oral glucocorticoid use, systemic absorption of nonoral glucocorticoid formulations can induce durable suppression of CRH and corticotropin relative to the duration and dose exposure. For example, inhaled fluticasone can induce glucocorticoid-induced adrenal insufficiency in a dose-dependent manner.[57-59] The prevalence of glucocorticoid-induced adrenal insufficiency in people who use inhaled glucocorticoids is 7.8% (95% CI, 4.2%-13.9%), but the prevalence increases with higher doses, such as fluticasone propionate, 500 µg or greater daily, for which the prevalence may be 21% (95% CI, 12%-35.5%), or a duration longer than 12 months, for which the prevalence may be 27.4% (95% CI, 17.7-39.8).[6] Similarly, intra-articular glucocorticoid injections repeated within 3 months can cause hypothalamic-pituitary-adrenal axis suppression.[6]

Most patients with glucocorticoid-induced adrenal insufficiency have been treated with supraphysiological glucocorticoids for months to years, which may lead to development of iatrogenic Cushing syndrome and glucocorticoid tolerance. When glucocorticoid therapy is no longer needed to treat a medical condition, the dose is tapered. During this process, patients frequently develop glucocorticoid withdrawal syndrome,[60,61] which usually occurs with supraphysiological glucocorticoid doses[62] (for example, when prednisone is decreased from 10 mg to 7.5 mg daily). Symptoms of glucocorticoid withdrawal syndrome, which include myalgias, arthralgias, fatigue, weakness, and mood changes, can be reduced by slowing the pace of the taper (eg, decreasing the dose every 2 weeks instead of weekly) or by using a taper that has smaller decrements in the daily glucocorticoid dose (eg, reducing prednisone by 1 mg instead of 2.5 mg or tapering to every-other-day regimens). It may be difficult to differentiate glucocorticoid withdrawal syndrome from adrenal insufficiency because their symptoms are similar. However, generally, glucocorticoid withdrawal syndrome is more likely than adrenal insufficiency if the glucocorticoid dose is supraphysiological.

Unlike most patients with primary or secondary adrenal insufficiency, patients with glucocorticoid-induced adrenal insufficiency can recover normal adrenocortical function and discontinue use of glucocorticoids. The process of tapering glucocorticoids with normalization of the hypothalamic-pituitary-adrenal axis may take months, and in some cases, years.[6] Monitoring of this tapering process involves checking morning serum cortisol levels 24 hours after the most recent glucocorticoid dose to avoid measurement of exogenous glucocorticoid metabolites. Recent clinical practice guidelines recommend discontinuing glucocorticoids in patients with glucocorticoid-induced insufficiency when morning serum cortisol is 10 µg/dL or higher.[6]

Patients with glucocorticoid-induced adrenal insufficiency can develop adrenal crisis if their steroid treatments are stopped suddenly or weaned too rapidly; studies have reported that 37% of patients with glucocorticoid-induced adrenal insufficiency developed at least 1 adrenal crisis and had more adrenal crises per person-year compared with patients with primary and secondary adrenal insufficiency.[12,21] However, patients with glucocorticoid-induced adrenal insufficiency are less likely to be prescribed injectable glucocorticoids for emergencies or to wear a medical alert identifier, and these patients report substantially more difficulty managing stress glucocorticoid dosing compared with patients with primary adrenal insufficiency or secondary adrenal insufficiency.[12,21] This phenomenon reflects less education for patients with glucocorticoid-induced adrenal insufficiency about how to increase steroid dosing during emergency situations, possibly due to the expectation that their adrenal insufficiency is temporary and because they are less likely to be treated by endocrinologists.[21]

Prognosis

After being diagnosed with adrenal insufficiency, starting steroid treatment, and being informed about the risk of and treatment for adrenal crisis, patients with adrenal insufficiency generally have very good quality of life and are capable of working, participating in sports, and traveling.[12,21] However, adrenal crisis can occur unexpectedly with concurrent illness or trauma and can lead to critical illness or death if not promptly treated with high doses of glucocorticoids and other supportive therapy (Table 3).

Special Considerations

Because 95% of cortisol is bound to corticosteroid-binding globulin or albumin, alterations in these proteins should be considered when assessing patients for adrenal insufficiency.

High Estrogen States

Estrogen markedly raises hepatic globulin production, including corticosteroid-binding globulin. Therefore, use of estrogen-containing oral contraceptives, hormone therapies, and pregnancy result in higher levels of total cortisol but relatively unchanged free cortisol fractions.[63-66] As a result, patients with high estrogen states may have the diagnosis of adrenal insufficiency erroneously excluded due to seemingly normal total cortisol levels. For these patients, measurement of total cortisol levels 1 month after

the high estrogen state has resolved may provide more accurate diagnostic information. Alternatively, measurement of free serum cortisol levels can be performed, although this test may be available only at specialized laboratories.

Low Serum Albumin or Protein Levels

Conversely, patients with very low protein levels (eg, albumin), such as with cirrhosis and chronic illness, may have much lower than normal total cortisol levels, although their free cortisol levels may be normal.[67] Therefore, patients with low albumin levels may be incorrectly diagnosed with adrenal insufficiency based on low total cortisol levels. For these patients, testing of serum free cortisol testing or salivary cortisol should be considered.[68-70]

Practical Considerations

Patient education about stress dosing of glucocorticoids should be reviewed at every clinic visit. Patients should be instructed to carry medical identification (such as an identification bracelet) and injectable glucocorticoids (eg, intramuscular or subcutaneous hydrocortisone, 100 mg) and trained how to use injectable glucocorticoids.[6,46] In the US, most ambulances and emergency medical services personnel do not carry hydrocortisone.[71]

Limitations

This Review has limitations. First, it is limited by the small number of randomized clinical trials that have evaluated the best approach to diagnosis and treatment. Second, there are no standardized definitions for adrenal insufficiency and adrenal crisis. Third, some relevant studies may have been missed. Fourth, the quality of included studies was not formally evaluated.

Conclusions

Although primary and secondary adrenal insufficiency are rare, glucocorticoid-induced adrenal insufficiency is a common condition. Diagnosis of adrenal insufficiency involves early-morning measurement of cortisol, corticotropin, and DHEAS. All patients with adrenal insufficiency should be treated with glucocorticoids and instructed about how to prevent and treat adrenal crisis.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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