Treatment of adrenal insufficiency in adults

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INTRODUCTION

Adrenal insufficiency is defined by inadequate cortisol production to meet physiologic needs. Primary adrenal insufficiency (Addison disease) results from disorders of the adrenal cortex, whereas secondary and tertiary adrenal insufficiency are due to dysfunction of the pituitary gland and the hypothalamus, respectively. Adrenal insufficiency leads to diffuse symptoms, may become life-threatening (adrenal crisis), and requires glucocorticoid replacement therapy. Primary adrenal insufficiency leads to both glucocorticoid (cortisol) and mineralocorticoid (principally aldosterone) deficiency. In contrast, central (ie, secondary or tertiary) adrenal insufficiency causes glucocorticoid, but not mineralocorticoid, deficiency because aldosterone is regulated primarily by the renin-angiotensin system, which is independent of the hypothalamus and pituitary. This distinction accounts for the different clinical presentation and management of these disorders.

The management of both acute and chronic adrenal insufficiency is reviewed here. The causes, clinical manifestations, and diagnosis of adrenal insufficiency in adults are reviewed separately. (See "Causes of primary adrenal insufficiency (Addison disease)" and "Clinical manifestations of adrenal insufficiency in adults" and "Diagnosis of adrenal insufficiency in adults".)

The management of adrenal insufficiency in children and in adults with classic congenital adrenal hyperplasia is also reviewed separately. (See "Treatment of adrenal insufficiency in children", section on 'Adrenal hormone replacement therapy' and "Treatment of classic

congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults", section on 'Continued adrenal hormone therapy'.)

ADRENAL CRISIS

Adrenal crisis is a life-threatening emergency that requires immediate treatment with parenteral glucocorticoids and isotonic fluid administration (table 1). Adrenal crisis denotes an episode of acute adrenal insufficiency and should be considered in any patient with shock. In addition to hypotension, patients commonly present with nonspecific signs and symptoms including nausea, vomiting, anorexia, fever, fatigue, weakness, and confusion or loss of consciousness. If adrenal crisis is suspected, treatment should be initiated immediately. Adrenal crisis occurs in patients with primary adrenal insufficiency and central adrenal insufficiency, but it is very uncommon in patients with adrenal insufficiency due to prolonged administration of exogenous glucocorticoids. (See "Clinical manifestations of adrenal insufficiency in adults", section on 'Adrenal crisis'.)

Clinical data evaluating the management of adrenal crisis are limited. Our approach is consistent with society guideline recommendations [1] and based on the pathophysiology of adrenal crisis, the pharmacology of available treatment options, and clinical experience.

Emergency management — Adrenal crisis requires urgent diagnosis and intervention (table 1). Treatment of patients who present in possible adrenal crisis should never be delayed to perform diagnostic tests. For all patients, initial treatment includes establishing intravenous (IV) access, isotonic fluid infusion, and parenteral glucocorticoid therapy. Laboratory tests (including serum electrolyte and glucose levels) should be sent. For patients without an established diagnosis of adrenal insufficiency, additional hormone measurements (cortisol, corticotropin [ACTH], aldosterone, renin) should be obtained to facilitate the diagnosis; however, these measurements do not alter emergency management and should never delay treatment initiation. The precipitating cause of adrenal crisis (eg, bacterial infection, viral gastroenteritis, trauma) should be determined and treated appropriately. (See "Clinical manifestations of adrenal insufficiency in adults", section on 'Precipitating factors'.)

The detailed steps of initial emergency management include:

- **Fluid resuscitation** – After IV access is established with a large-gauge needle, we administer at least 1 liter of 0.9 percent saline or 5 percent dextrose in 0.9 percent saline within one hour. This fluid bolus may need to be repeated, as patients with adrenal crisis usually require at least 2 to 3 liters of isotonic fluids within the first 12 to 24 hours. Once

the patient is volume resuscitated, maintenance fluids are administered as for the general medical population, which is discussed elsewhere. (See "Maintenance and replacement fluid therapy in adults", section on 'Maintenance fluid therapy'.)

We avoid hypotonic saline because it can worsen hyponatremia. Lactated Ringer solution also theoretically may worsen hyponatremia, although clinical data are limited.

- **Initial laboratory tests** – Although initial laboratory tests are sent at the time of first clinical suspicion for adrenal crisis, presumptive management should not be delayed pending results.

  - **All patients in adrenal crisis** – In all patients in known or suspected adrenal crisis, we measure serum creatinine, blood urea nitrogen (BUN), electrolyte, and glucose levels to evaluate for hyponatremia, hyperkalemia, and hypoglycemia. (See "Hyponatremia and hyperkalemia in adrenal insufficiency" and "Clinical manifestations of adrenal insufficiency in adults", section on 'Laboratory findings'.)

  - **Additional testing for patients without a prior diagnosis of adrenal insufficiency** – Prior to initiation of glucocorticoid therapy, additional laboratory tests should be sent for patients without an established diagnosis of adrenal insufficiency. For all patients without a prior diagnosis, we send a serum cortisol level to verify cortisol deficiency. When clinical suspicion is high for adrenal insufficiency, we also measure plasma levels of ACTH, aldosterone, and renin to initiate the etiologic evaluation. (See "Determining the etiology of adrenal insufficiency in adults", section on 'Establish the level of defect'.)

- **Glucocorticoid therapy** – For patients who present in known or suspected adrenal crisis, we recommend immediate administration of hydrocortisone (100 mg IV bolus), followed by 50 mg IV every six hours (or 200 mg/24 hours as a continuous IV infusion) for the first 24 hours [2]. We then reduce the hydrocortisone dose to 50 mg IV every 12 hours. Continued taper is guided by the patient's clinical status. (See 'Subsequent management' below.)

  We prefer hydrocortisone because it has both glucocorticoid and mineralocorticoid activity; this is particularly important in patients with known primary adrenal insufficiency or those with serum potassium >6.0 mEq/L and/or clear evidence of volume depletion, which may indicate mineralocorticoid deficiency. If hydrocortisone is unavailable, alternatives include methylprednisolone 40 mg IV or dexamethasone 4 to 6 mg IV (table 1).

- **Mineralocorticoid therapy for patients with known or suspected primary adrenal insufficiency**

  - **Concurrent hydrocortisone treatment** – In patients with known or suspected primary adrenal insufficiency (eg, based on the presence of hyperkalemia, skin hyperpigmentation, or overt volume depletion), fludrocortisone is unnecessary during high-dose hydrocortisone therapy with isotonic fluid administration. At doses ≥40 mg daily, hydrocortisone has sufficient mineralocorticoid activity to serve as replacement therapy. In such patients, fludrocortisone should be resumed or initiated during hydrocortisone taper when oral intake is possible. (See 'Patients with known adrenal insufficiency' below.)

  - **Concurrent treatment with methylprednisolone or dexamethasone** – In patients with known or suspected primary adrenal insufficiency, we add oral fludrocortisone 0.2 mg daily during methylprednisolone or dexamethasone therapy. Methylprednisolone has less mineralocorticoid activity than hydrocortisone, and dexamethasone has none. Therefore, patients with primary adrenal insufficiency usually require mineralocorticoid replacement. (See 'Patients with known adrenal insufficiency' below.)

- **Electrolyte management** – Hyponatremia and hypoglycemia can evolve consequent to cortisol deficiency, whereas the presence of hyperkalemia indicates mineralocorticoid as well as glucocorticoid deficiency.

  - **Hyponatremia** – If hyponatremia is present and the patient is known to have central adrenal insufficiency, free thyroxine (T4) should be measured to exclude concurrent central hypothyroidism. The serum sodium level should be monitored closely (eg, every two to six hours) until normalization. Parenteral hydrocortisone therapy and isotonic fluid administration correct hyponatremia due to adrenal insufficiency. If hyponatremia persists despite these interventions, it is not due to adrenal insufficiency, and additional evaluation is needed to determine the cause. (See "Diagnostic evaluation of adults with hyponatremia".)

  - **Hyperkalemia** – Parenteral hydrocortisone and volume replacement will correct hyperkalemia, and additional intervention is not typically necessary. If present, hyperkalemia should correct within a few hours of hydrocortisone initiation. If hyperkalemia persists, additional intervention and evaluation for alternative causes are needed. (See "Causes and evaluation of hyperkalemia in adults" and "Treatment and prevention of hyperkalemia in adults".)

- **Hypoglycemia** – Isotonic, dextrose-containing fluids should be administered to patients with known or suspected hypoglycemia. Additional dextrose should be administered acutely if hypoglycemia is severe enough to cause neuroglycopenia (ie, glucose <55 mg/dL [<3 mmol/L]). The glucose-raising effect of supraphysiologic glucocorticoid treatment is potent, and correction of hypoglycemia is not sufficient to confirm adrenal insufficiency as the underlying cause. (See "Hypoglycemia in adults with diabetes mellitus", section on 'Reversing hypoglycemia' and "Hypoglycemia in adults without diabetes mellitus: Clinical manifestations, causes, and diagnosis", section on 'Causes of hypoglycemia'.)

Expected treatment response — If hypotension is caused by adrenal crisis, it should improve rapidly (within a few hours) with parenteral glucocorticoid therapy and isotonic fluid administration. If hypotension persists despite these interventions, the precipitating cause of the adrenal crisis may not be adequately addressed, or the patient may have an alternative cause of hypotension and shock. (See "Clinical manifestations of adrenal insufficiency in adults", section on 'Precipitating factors' and "Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock", section on 'Common conditions needing lifesaving interventions'.)

Subsequent management — After initial, emergency treatment of adrenal crisis, further adrenal hormone replacement and evaluation depend in part on whether the patient has a prior diagnosis of adrenal insufficiency. Assessment of the patient's volume status and urine output should guide subsequent fluid administration. (See "Maintenance and replacement fluid therapy in adults".)

All patients require close outpatient follow-up within one to two weeks of hospital discharge for counseling, assessment of risk factors for recurrent adrenal crisis, and, for patients without a known history of adrenal insufficiency, further diagnostic evaluation.

Patients with known adrenal insufficiency — Once stable, patients with known adrenal insufficiency generally transition to their home treatment regimen.

- **Glucocorticoid therapy** – We taper hydrocortisone over one to three days unless a major complicating illness requires prolonged treatment with high-dose parenteral therapy. If the patient has ongoing illness (eg, infection with moderate to severe symptoms, postsurgical complications), we first transition to an oral stress dose regimen; otherwise, we resume the patient's usual maintenance regimen. Stress dose and maintenance glucocorticoid regimens are discussed in detail below. (See 'Circumstances requiring

glucocorticoid dose adjustment' below and 'Hydrocortisone (preferred glucocorticoid)' below.)

- **Mineralocorticoid therapy** – For patients with known primary adrenal insufficiency, we reinitiate their usual maintenance fludrocortisone dose when the hydrocortisone dose is tapered below 40 mg daily, which confers mineralocorticoid activity roughly equivalent to 0.1 mg fludrocortisone [1]. Mineralocorticoid replacement therapy is rarely needed in patients with central adrenal insufficiency and is reviewed in detail below. (See 'Mineralocorticoid replacement for selected individuals' below.)

Patients without known adrenal insufficiency — For patients without a prior diagnosis of adrenal insufficiency, the initial serum cortisol level usually is available within a few hours and may help verify or exclude cortisol deficiency. However, presumptive management of clinically suspected adrenal insufficiency should **not** be delayed pending results. The interpretation of serum cortisol level in the setting of adrenal crisis is reviewed separately. (See "Diagnosis of adrenal insufficiency in adults", section on 'Suspected adrenal crisis'.)

- **Glucocorticoid therapy**

  - **Adrenal insufficiency likely or cannot be excluded** – For patients in whom underlying adrenal insufficiency is likely or cannot be excluded, we continue maintenance glucocorticoid replacement until the patient undergoes further diagnostic evaluation, usually in the outpatient setting. (See "Diagnosis of adrenal insufficiency in adults", section on 'ACTH stimulation tests'.)

    Once the patient has stabilized, we taper hydrocortisone over one to three days, unless a major complicating illness requires prolonged treatment with high-dose parenteral therapy. If the patient has ongoing illness (eg, infection with moderate to severe symptoms, postsurgical complications), we first transition to an oral stress dose regimen; otherwise, we initiate a maintenance glucocorticoid replacement regimen. (See 'Circumstances requiring glucocorticoid dose adjustment' below and 'Hydrocortisone (preferred glucocorticoid)' below.)

  - **Adrenal insufficiency excluded** – For patients in whom underlying adrenal insufficiency is excluded, we taper and discontinue hydrocortisone over one to three days.

- **Patient education and counseling** – Prior to hospital discharge, patients with known or suspected adrenal insufficiency should receive counseling about glucocorticoid

replacement, the risks of cortisol deficiency, emergency measures, and circumstances requiring glucocorticoid dose adjustments. (See 'Patient education and safety' below.)

- **Mineralocorticoid therapy for selected patients** – If other initial diagnostic laboratory tests (aldosterone, renin, ACTH) have not returned, we initiate maintenance mineralocorticoid replacement with fludrocortisone empirically in patients who presented with hyperkalemia, skin hyperpigmentation, or overt volume depletion; these are signs of mineralocorticoid deficiency and therefore may indicate primary adrenal insufficiency. In these patients, we begin fludrocortisone when the hydrocortisone dose is tapered below 40 mg daily, which confers mineralocorticoid activity roughly equivalent to 0.1 mg fludrocortisone [1]. (See 'Mineralocorticoid replacement for selected individuals' below.)

  In patients who did not present with hyperkalemia or volume depletion, we monitor blood pressure and serum electrolyte levels closely during hydrocortisone taper and initiate fludrocortisone only if indicated by hypotension, orthostasis, or hyperkalemia. Fludrocortisone dosing and treatment monitoring are reviewed in detail below. (See 'Mineralocorticoid replacement for selected individuals' below.)

  If the diagnostic test results are available, they can be used to determine the presence of primary adrenal insufficiency and attendant need for mineralocorticoid replacement. (See "Determining the etiology of adrenal insufficiency in adults", section on 'Establish the level of defect'.)

- **Additional diagnostic and etiologic evaluation** – In patients with an indeterminate or low serum cortisol level, we verify cortisol deficiency and, if indicated, determine its cause once the patient's condition is stable. This evaluation is usually performed in the outpatient clinic setting and is reviewed separately. (See "Diagnosis of adrenal insufficiency in adults" and "Determining the etiology of adrenal insufficiency in adults".)

CHRONIC ADRENAL INSUFFICIENCY

Sequence of hormone replacement therapy

- **Primary adrenal insufficiency** – In patients with primary adrenal insufficiency, glucocorticoid and mineralocorticoid replacement are started concurrently upon diagnosis (algorithm 1). Selection of initial glucocorticoid and mineralocorticoid regimens is reviewed below. (See 'Glucocorticoid replacement for all patients' below and 'Mineralocorticoid replacement for selected individuals' below.)

In primary adrenal insufficiency, plasma dehydroepiandrosterone (DHEA and DHEA sulfate [DHEAS]) levels are usually low. The optimal use of DHEA therapy and its risk and benefits are uncertain. In females with persistent symptoms suggestive of androgen deficiency, a therapeutic trial of androgen replacement with DHEA may be offered. (See 'Androgen replacement therapy for selected females' below.)

- **Central adrenal insufficiency** – In patients with central (ie, secondary or tertiary) adrenal insufficiency, glucocorticoid replacement therapy is started upon diagnosis (algorithm 1). Selection of an initial glucocorticoid regimen is reviewed below. (See 'Glucocorticoid replacement for all patients' below.)

  Once this regimen is optimized, we assess females for persistent symptoms suggestive of androgen deficiency. If such symptoms are present, a therapeutic trial of androgen replacement with DHEA may be offered. (See 'Androgen replacement therapy for selected females' below.)

  The initiation of glucocorticoid therapy requires additional considerations for patients with central adrenal insufficiency. Such patients require evaluation for other pituitary hormone deficiencies [3]. In patients with more than one pituitary hormone deficiency, glucocorticoid therapy should be initiated prior to other hormone replacement therapies, particularly thyroid or growth hormone replacement. The evaluation for hypopituitarism is reviewed separately. (See "Diagnostic testing for hypopituitarism".)

  - **Concurrent hypothyroidism** – In patients with hypopituitarism who also have secondary hypothyroidism, glucocorticoid replacement must precede thyroid hormone replacement. Thyroid hormone administration without adequate glucocorticoid replacement can precipitate adrenal crisis through accelerated cortisol metabolism mediated by 11-beta-hydroxysteroid dehydrogenase type 2 (11-beta-HSD2).

  - **Concurrent growth hormone deficiency** – In patients with hypopituitarism who also have growth hormone deficiency, glucocorticoid replacement therapy must be optimized before initiation of growth hormone therapy. Patients with corticotropin (ACTH) deficiency who receive suboptimal glucocorticoid replacement are at risk for overt cortisol deficiency when growth hormone therapy is initiated. This risk is due to the inhibitory effect of growth hormone on 11-beta-hydroxysteroid dehydrogenase type 1 (11-beta-HSD1), the enzyme that converts cortisone to cortisol [4].

Glucocorticoid replacement for all patients — Cortisol deficiency is a feature of primary and central adrenal insufficiency, so any form of adrenal insufficiency requires glucocorticoid replacement therapy. Continual patient education and counseling are essential facets of

management because cortisol deficiency can be life-threatening, and glucocorticoid replacement regimens must be adjusted during periods of stress. Rare patients can have partial central adrenal insufficiency, defined as normal basal cortisol secretion with inadequate cortisol response to stress. In such patients, chronic daily glucocorticoid replacement may not be necessary, but patients should be educated about signs of adrenal insufficiency that may develop during stress and instructed on stress dose glucocorticoid management. Whenever possible, these individuals should be under the care of a specialist experienced in the treatment of partial central adrenal insufficiency. (See 'Patient education and safety' below and 'Circumstances requiring glucocorticoid dose adjustment' below.)

Glucocorticoid replacement regimens are generally the same for patients with primary or central adrenal insufficiency [5-7]. Chronic excess exposure to glucocorticoids can result in iatrogenic Cushing syndrome. Therefore, a critical goal of replacement therapy is to provide adequate but not excessive glucocorticoid exposure. Close monitoring for signs and symptoms of both over- and undertreatment is required for all patients on glucocorticoid therapy. The optimal glucocorticoid dose for any patient is the lowest dose that relieves symptoms of cortisol deficiency. (See 'Glucocorticoid therapy monitoring' below and "Epidemiology and clinical manifestations of Cushing syndrome".)

In adults with adrenal insufficiency due to classic congenital adrenal hyperplasia, glucocorticoid therapy has additional goals and is reviewed separately. (See "Treatment of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults", section on 'Continued adrenal hormone therapy'.)

Hydrocortisone (preferred glucocorticoid) — For most patients with adrenal insufficiency, we suggest hydrocortisone for glucocorticoid replacement therapy [1]. Few data are available to guide the selection of glucocorticoid replacement regimens. Consequently, regimens should be individualized with close monitoring to ensure that treatment goals are met.

Rationale — Hydrocortisone is a short-acting agent and allows dose titration in small increments. Dosing regimens also can be adjusted to provide variable glucocorticoid exposure over the course of a day. Hydrocortisone is usually administered in two or three daily divided doses to better mimic the circadian pattern of endogenous cortisol secretion, with an early morning peak and a bedtime nadir for individuals who follow a natural circadian sleep-wake schedule.

When hydrocortisone therapy is unavailable, the short-acting agent cortisone acetate is a reasonable alternative. (See 'Alternative short-acting therapy' below.)

For individuals with difficulty adhering to multiple daily hydrocortisone doses or those with persistent symptoms on hydrocortisone regimens, once-daily therapy with prednisolone may provide greater ease of dosing and symptom relief. (See 'Longer-acting agents for adherence challenges or persistent symptoms' below.)

Initial dosing — We use an initial hydrocortisone dose of 15 to 25 mg daily divided in two or three doses; alternatively, a calculated daily dose of 10 to 12 mg/m^2 body surface area can be used. The first dose should be administered in the morning upon waking, and the last dose is administered at least four to six hours before bedtime [1]. Most regimens avoid mid-to-late evening doses because endogenous cortisol production is minimal from approximately 6:00 PM to 3:00 AM.

- In a typical twice-daily regimen, approximately two-thirds of the total daily dose is taken in the morning and one-third in the afternoon.
- Three times daily regimens entail decreasing doses in the morning, midday, and late afternoon (eg, hydrocortisone 10, 5, and 2.5 mg taken at 7:00 AM, 12:00 PM, and 4:00 PM, respectively).

The bioavailability of hydrocortisone is nearly 100 percent, and serum cortisol concentrations rise rapidly in the 30 minutes or so after ingestion. Thus, appropriate dosing can be predicted reasonably well, and hydrocortisone can be taken immediately upon waking without a prolonged delay in effect. Body weight and concurrent medications may influence selection of an initial hydrocortisone dose. (See 'Special considerations for dosing' below.)

Dose titration

- **Total daily dose** – The initial hydrocortisone dose should be titrated as needed based on clinical monitoring for evidence of under- or overtreatment. The ideal dose is the lowest total daily dose that alleviates symptoms of cortisol deficiency. If indicated, dose adjustments should be small (eg, 2.5 to 5 mg increments), and patients should be monitored closely during dose titration. In patients taking fludrocortisone, the adequacy of mineralocorticoid replacement should be assessed before the hydrocortisone dose is increased. (See 'Glucocorticoid therapy monitoring' below and 'Mineralocorticoid therapy monitoring' below.)
- **Number of daily doses** – For most patients, we initiate twice or three-times daily hydrocortisone dosing. Although some patients do well on a single daily dose of hydrocortisone, we reserve single-dose regimens for those who have difficulty adhering to the afternoon dose.

Some patients on a twice-daily regimen develop isolated early morning or late evening symptoms of cortisol deficiency. In such patients, we add a third, small dose (eg, 2.5 mg) in the early evening without increasing the total daily dose. Three times daily dosing may help alleviate symptoms of cortisol deficiency and mimics the day-curve of cortisol seen in healthy volunteers [8]. Some patients may benefit from a dosing frequency greater than three times daily for short-acting glucocorticoids [9]. As an alternative strategy to alleviate early morning symptoms, patients may set an overnight alarm and take the morning hydrocortisone dose a few hours prior to rising. Early morning symptoms can occur because immediate-release, short-acting glucocorticoid therapy cannot replicate a normal, diurnal rhythm, in which endogenous serum cortisol concentrations already would have reached or passed the circadian peak before people would typically take the morning glucocorticoid dose. This transient early morning cortisol deficiency probably accounts for the symptoms of fatigue, lassitude, mild nausea, and headache that are often present upon waking and relieved within 30 to 60 minutes after the morning hydrocortisone dose.

- **Rationale for divided doses** – In one study, quality of life and patient preference were greater with a split dose regimen (20 mg at 7:00 AM and 10 mg at 7:00 PM) compared with a single total dose in the morning or evening [10]. No studies have compared quality of life with two- versus three-dose daily regimens. Smaller, divided doses of hydrocortisone also may help avoid excessive cortisol exposure and adverse side effects of therapy [11]. Higher doses of hydrocortisone (those resulting in cortisol levels ≥25 mcg/dL) exceed the binding capacity of corticosteroid-binding globulin (CBG) and lead to increases in serum free cortisol followed by rapid filtration into urine [12]. In contrast, smaller, divided hydrocortisone doses prevent this increase in free cortisol even when administered at the same total daily dose [13].

Alternative regimens

Alternative short-acting therapy — Cortisone acetate is a short-acting glucocorticoid and is a reasonable alternative to hydrocortisone for glucocorticoid replacement therapy. In some regions, cortisone acetate is the only available short-acting glucocorticoid, and individual patients may prefer cortisone acetate to hydrocortisone. Cost is another key consideration for choice of initial therapy.

An initial replacement regimen of cortisone acetate is 20 to 35 mg administered in two or three daily divided doses (eg, 15, 5, and 2.5 mg). Like hydrocortisone, the first dose is administered immediately upon waking, and the final dose is taken at least four to six hours before bedtime.

In contrast to hydrocortisone, cortisone acetate is a precursor that must undergo hepatic conversion to cortisol via 11-beta-HSD1 and therefore could lead to more variability in dosing requirements. For this reason, we prefer hydrocortisone as initial therapy. However, this potential limitation has not been studied carefully.

Longer-acting agents for adherence challenges or persistent symptoms — Longer-acting glucocorticoids may be useful for patients who have difficulty adhering to multiple daily dosing regimens or those who experience severe symptoms of cortisol deficiency in the late evening or early morning on short-acting glucocorticoid regimens. Longer-acting glucocorticoids provide a smoother physiological effect and avoid the marked changes in serum glucocorticoid levels that occur with short-acting drugs (table 2). Treatment options include the following:

- **Prednisolone (preferred longer-acting agent)** – If a longer-acting glucocorticoid is used for replacement therapy, we prefer the intermediate-acting agent prednisolone. The usual oral replacement dose for prednisolone is 3 to 5 mg daily, administered as either a single dose taken in the morning upon waking or two divided doses (approximately 70 to 80 percent of the dose taken in the morning and the remainder at bedtime).

- **Prednisone** – Prednisone is also an intermediate-acting glucocorticoid. The usual initial replacement dose for prednisone is 5 mg administered orally once daily, and the typical dosing range is 2.5 to 7.5 mg daily. Like cortisone acetate, prednisone requires activation by 11-beta-HSD1 to confer biological effects and could lead to more variability in dosing requirements. Prednisolone is therefore preferred to prednisone if a longer-acting glucocorticoid is indicated.

- **Dexamethasone** – Dexamethasone is a long-acting glucocorticoid. The usual initial replacement dose is 0.5 mg administered orally once daily, with a typical dosing range of 0.25 to 0.75 mg daily. Dexamethasone has several limitations as glucocorticoid replacement therapy, including its long duration of action, limited flexibility for dose titration, and variable interindividual metabolism, leading to higher potential for overtreatment. Nonetheless, much of the clinical evidence supporting this heightened risk of overtreatment is anecdotal and from an era when higher glucocorticoid doses were commonly prescribed.

- **Modified-release formulations (limited availability)** – Modified-release forms of hydrocortisone are commercially available in some regions of the world but not the United States. If available, modified-release hydrocortisone is a reasonable alternative to immediate-release hydrocortisone. A once-daily dual-release hydrocortisone tablet is

authorized for use in the European Union. This formulation combines an immediate-release coating with an extended-release core and provides a more physiologic serum cortisol profile than three times daily hydrocortisone [14]. Like longer-acting glucocorticoids, these formulations provide greater ease of dosing, while their modified release enables better approximation of the circadian pattern of endogenous cortisol production. Short-term data from randomized studies support the potential for modified-release hydrocortisone to impart metabolic benefits (eg, lower body weight and blood pressure) relative to conventional therapy [15-17].

A long-acting hydrocortisone formulation is authorized for use in the United Kingdom and European Union for treatment of primary adrenal insufficiency specifically due to classic congenital adrenal hyperplasia. The treatment of primary adrenal insufficiency in adults with classic congenital adrenal hyperplasia is reviewed in detail separately. (See "Treatment of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults", section on 'Glucocorticoid therapy for all patients'.)

Special considerations for dosing

- **Body weight** – We generally initiate glucocorticoid therapy at the low end of the usual dosing range for patients with lower body weight (eg, <75 kg) and at the high end for patients with higher body weight (eg, >115 kg). (See 'Initial dosing' above.)

  For some patients with low body weight (eg, <55 kg), a total daily dose as low as hydrocortisone 10 mg is sufficient [18]. Pharmacokinetic studies are needed to better guide body weight-based glucocorticoid dosing for adrenal insufficiency. As for any patient, we tailor treatment to achieve the lowest dose that alleviates symptoms of cortisol deficiency. (See 'Glucocorticoid therapy monitoring' below.)

- **Concomitant medications** – Glucocorticoids are metabolized by the cytochrome P450 3A4 enzyme (CYP3A4). Therefore, in patients taking medications that affect CYP3A4 activity, glucocorticoid regimens may require dose adjustments [19,20]. Glucocorticoid doses may need to be increased in patients taking drugs that induce CYP3A4 metabolism, such as phenytoin, barbiturates, rifampin, phenobarbital, and mitotane [21-24]. In contrast, CYP3A4 inhibitors may require glucocorticoid dose reductions to avoid excess exposure. Inhibitors of CYP3A4 include clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, and grapefruit (table 3).

Glucocorticoid therapy monitoring — Glucocorticoid replacement therapy is monitored through clinical assessments rather than biochemical tests. Patients should be assessed at least once every three months early after diagnosis and during dose titration and at least once

annually after a stable replacement regimen is established. We suggest using the lowest glucocorticoid dose that relieves symptoms of cortisol deficiency.

- **Clinical assessment** – Routine clinical assessments include measurement of blood pressure, heart rate, and body weight, as well as detailed symptom queries about appetite, energy, daytime somnolence, nausea, ability to concentrate, changes in body weight, and fatigue. At each visit, we ask patients about therapy adherence as well as the need to administer additional glucocorticoid doses for intercurrent illnesses or other stressors. Ongoing patient counseling is a critical facet of treatment monitoring. (See 'Patient education and safety' below.)

  - **Evidence of undertreatment** – Signs and symptoms that suggest undertreatment include lethargy, subjective weakness, low blood pressure, nausea, weight loss, and poor appetite. Any of these could indicate that the glucocorticoid dose is too low. When these signs or symptoms are present, we increase the glucocorticoid dose by 2.5 to 5 mg and monitor the patient closely. If the signs or symptoms are not promptly (eg, within a week) improved, they are not due to cortisol deficiency, and we resume the lower glucocorticoid dose.

    Symptoms that occur only at a specific, predictable time of day (eg, early morning or late evening) may indicate a need for a change in the timing or frequency of glucocorticoid dosing rather than an increase in the total daily dose. (See 'Dose titration' above.)

  - **Evidence of overtreatment** – Signs and symptoms suggestive of overtreatment include body weight gain, increased blood pressure, impaired sleep, edema, facial plethora, and other manifestations of Cushing syndrome. These are reviewed in detail separately. (See "Epidemiology and clinical manifestations of Cushing syndrome", section on 'Categories of clinical manifestations'.)

    For patients taking hydrocortisone or cortisone acetate with evidence of overtreatment, we reduce the total daily dose in 2.5 to 5 mg increments. We monitor patients closely both for resolution of signs or symptoms of overtreatment and for emergence of signs or symptoms of cortisol deficiency. Chronic overtreatment can lead to complications of glucocorticoid excess including dysglycemia, hypertension, dyslipidemia, and increased cardiovascular risk. Excessive glucocorticoid therapy also may increase risk of osteoporosis [25,26].

- **Limited role for biochemical assessment** – We monitor treatment through clinical rather than biochemical assessments (eg, measurement of plasma ACTH or cortisol

concentration) [1]. Reports suggest that clinical assessment alone works equally well [27]. Biochemical testing may be helpful in rare circumstances of suspected glucocorticoid malabsorption (eg, individuals with persistent clinical evidence of adrenal insufficiency despite progressive glucocorticoid dose titration). In such individuals, we measure serum cortisol one hour after the morning dose of hydrocortisone [28].

In patients with primary adrenal insufficiency, measurement of early morning plasma ACTH concentration is not necessary for routine monitoring but may help detect overreplacement. In such patients, a low-normal or suppressed morning plasma ACTH concentration indicates glucocorticoid overtreatment. However, an elevated concentration does not generally indicate undertreatment. Early morning cortisol deficiency is evident with immediate-release hydrocortisone therapy and results in plasma ACTH concentrations that are elevated two- to eightfold for several hours in the early morning, with sustained elevation for several hours after the first hydrocortisone dose is taken [4,29,30]. In patients with central adrenal insufficiency, measurements of plasma ACTH concentration are not helpful, because levels are expected to be low and do not reflect tissue cortisol sufficiency.

Although some advocate the use of normative day-curve or single timepoint cortisol values to assess the adequacy of hydrocortisone therapy [8,28], these have not been incorporated into routine clinical practice.

Mineralocorticoid replacement for selected individuals

Primary adrenal insufficiency (all patients) — In patients with primary adrenal insufficiency, we assess mineralocorticoid deficiency both clinically and through measurement of aldosterone and renin levels [1]. A low aldosterone level with a plasma renin activity (PRA) above the upper limit of the reference range confirms mineralocorticoid deficiency. Although virtually all patients with primary adrenal insufficiency require mineralocorticoid replacement, rare patients with mild mineralocorticoid deficiency do not need replacement therapy or achieve sufficient mineralocorticoid replacement through hydrocortisone therapy alone.

Initial dosing — For patients with confirmed mineralocorticoid deficiency, we initiate fludrocortisone 0.05 to 0.1 mg daily. Selecting a dose within this range depends on the glucocorticoid replacement regimen, as different agents have variable mineralocorticoid activity. Patients do **not** need to restrict their dietary sodium intake during fludrocortisone therapy.

- **For individuals taking hydrocortisone or cortisone acetate** – For individuals taking hydrocortisone or cortisone acetate, we generally choose an initial dose of fludrocortisone

0.05 mg daily because these agents have some mineralocorticoid activity, and the lower fludrocortisone dose may be adequate. The dose is then titrated based on both clinical and biochemical assessments, including PRA. In rare patients, hydrocortisone alone is sufficient for mineralocorticoid replacement. Such individuals can develop signs of mineralocorticoid overtreatment (eg, hypertension, hypokalemia) with fludrocortisone doses as low as 0.05 mg twice weekly. (See 'Mineralocorticoid therapy monitoring' below.)

- **For individuals taking prednisolone, prednisone, or dexamethasone** – For individuals taking prednisolone, prednisone, or dexamethasone, we start fludrocortisone 0.1 mg daily. Prednisolone and prednisone have weaker mineralocorticoid activity than hydrocortisone and dexamethasone has none, so higher fludrocortisone doses are usually needed with these agents. The initial fludrocortisone dose is then titrated based on both clinical and biochemical assessments, including PRA. Patients receiving dexamethasone may require up to 0.2 mg daily of fludrocortisone to lower their PRA to the upper reference range [31,32]. (See 'Mineralocorticoid therapy monitoring' below.)

Dose adjustments for increased salt losses or primary hypertension — The fludrocortisone dose and/or dietary sodium intake may need adjustment in individuals who regularly engage in vigorous exercise, are exposed to warm climates, or develop primary hypertension during treatment.

- **Vigorous exercise or warm climates** – When increased salt losses occur, patients may need to increase their dietary sodium intake and/or fludrocortisone dose to prevent symptoms of mineralocorticoid deficiency. When patients engage in vigorous exercise, salt loss through perspiration is transient, and increased fluid and dietary sodium intake alone is usually sufficient to prevent symptoms of mineralocorticoid deficiency. Patients who engage in prolonged exercise (eg, long-distance running or cycling) may need to increase the fludrocortisone dose on days when the exercise is performed.

  During the summer or in warmer climates when salt loss in perspiration increases throughout the day, the fludrocortisone dose may need to be increased by 50 to 100 percent. We empirically increase the dose if a patient is routinely exposed to temperatures above approximately 29°Celsius (85°F). Alternatively, salt tablets may be used to provide an additional 1 to 2 g sodium daily.

- **Hypertension** – In patients with primary adrenal insufficiency who develop primary hypertension (formerly called "essential" hypertension), the initial approach is dietary sodium restriction and a reduced dose of fludrocortisone [33,34]. Primary hypertension should only be diagnosed if glucocorticoid and mineralocorticoid overtreatment are

excluded as causes of blood pressure elevation. (See 'Glucocorticoid therapy monitoring' above and 'Mineralocorticoid therapy monitoring' below.)

Mineralocorticoid therapy usually cannot be discontinued without risking sodium depletion. Therefore, if hypertension is not adequately managed on the reduced fludrocortisone dose, we continue fludrocortisone and initiate antihypertensive treatment. If an antihypertensive medication is needed, diuretics, eplerenone, or spironolactone should **not** be used, since they partly or completely antagonize fludrocortisone action. First-line treatments include angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEs). Dihydropyridine calcium channel blockers are a reasonable alternative.

Mineralocorticoid therapy monitoring — In patients with mineralocorticoid deficiency, both clinical and biochemical assessments are needed to assess the adequacy of mineralocorticoid replacement therapy. These assessments are performed at least every one to three months during treatment initiation or dose adjustments and at least annually in individuals on stable replacement regimens.

- **Clinical assessment** – Clinical monitoring includes queries about symptoms of fatigue, lightheadedness, nausea, muscle cramping, and salt craving. Routine monitoring also includes measurement of supine and upright blood pressure and heart rate to assess for postural hypotension. Hypertension and edema are signs of excessive mineralocorticoid replacement [33]. (See "Pathophysiology and clinical features of primary aldosteronism", section on 'Clinical features'.)

- **Biochemical assessment** – Biochemical monitoring includes measurement of the serum sodium, potassium, and creatinine concentrations and PRA. We adjust the fludrocortisone dose to lower the PRA to the upper reference range [31,32]. If direct renin concentration (DRC) is measured instead of PRA, targeting a DRC that is within the reference range or mildly elevated is reasonable.

  We remeasure PRA three months after initiating fludrocortisone therapy or sooner if patients report any signs or symptoms of under- or overtreatment. If indicated, we titrate the fludrocortisone dose in 0.05 mg increments as needed to achieve the target PRA. Once a stable fludrocortisone dose is achieved, we measure PRA annually in all patients and whenever a patient develops signs or symptoms of mineralocorticoid deficiency or excess. Normal morning PRA for seated, healthy individuals with a typical dietary sodium intake ranges from approximately 1 to 4 ng/mL per hour (0.8 to 3 nmol/L per hour).

A PRA in the upper reference range usually is associated with a normal serum potassium level and alleviation of symptoms of mineralocorticoid deficiency. However, if PRA remains elevated but the patient is asymptomatic and the serum potassium is normal, the fludrocortisone dose should **not** be increased to normalize PRA. In this setting, increasing the fludrocortisone dose imparts risk of hypokalemia and edema [35]. (See "Assays of the renin-angiotensin-aldosterone system in adrenal disease", section on 'Renin'.)

- **Discerning between glucocorticoid- and mineralocorticoid mediated effects** – The clinical signs and symptoms of over- or undertreatment with glucocorticoid and mineralocorticoid therapy can overlap. Biochemical measurements and careful clinical assessment can help distinguish between glucocorticoid- or mineralocorticoid-mediated effects.

  - **Signs or symptoms of overtreatment** – Edema and hypertension may indicate either glucocorticoid or mineralocorticoid overtreatment. In such cases, the presence of hypokalemia and/or a PRA that is below the upper third of the reference range suggest mineralocorticoid overtreatment. Conversely, concurrent signs of glucocorticoid overtreatment (eg, weight gain, increased appetite, impaired sleep) strongly suggest glucocorticoid rather than mineralocorticoid overtreatment. In patients with primary adrenal insufficiency, an early morning plasma ACTH level that is suppressed or in the lower third of the reference range further indicates glucocorticoid overtreatment.

  - **Signs or symptoms of undertreatment** – Lightheadedness, postural hypotension, nausea, weakness, and fatigue may indicate either glucocorticoid or mineralocorticoid undertreatment. In such cases, the presence of salt craving, hyperkalemia, and/or a PRA that is above the reference range suggest mineralocorticoid undertreatment. Conversely, diminished appetite and weight loss strongly suggest glucocorticoid undertreatment. In this setting, a plasma ACTH level is not helpful for distinguishing between glucocorticoid and mineralocorticoid undertreatment.

Central adrenal insufficiency (rarely needed) — Mineralocorticoid replacement is rarely required in patients with central adrenal insufficiency because ACTH is not the main physiological regulator of aldosterone secretion. Rare patients with longstanding disease eventually may require replacement therapy with fludrocortisone. Lightheadedness, weakness, salt craving, mild nausea, and postural hypotension are signs and symptoms of mineralocorticoid deficiency. The diagnosis is confirmed with findings of an elevated renin level or PRA and low aldosterone level. If indicated, replacement therapy with fludrocortisone is the same as for individuals with primary adrenal insufficiency. (See 'Primary adrenal insufficiency (all patients)' above.)

Androgen replacement therapy for selected females — In most forms of adrenal insufficiency, serum concentrations of DHEA are extremely low, as the adrenal cortex is the primary source of androgens including DHEA and DHEA sulfate (DHEAS). In selected females with adrenal insufficiency, androgen replacement therapy may be beneficial for mood, quality of life, or libido.

Indications

- **Females** – We suggest a trial of DHEA treatment in females with adrenal insufficiency who have significant symptoms of depression or anxiety, low libido or energy, or impaired sense of well-being despite optimized glucocorticoid and mineralocorticoid (if applicable) therapy. We typically offer a therapeutic trial to females with persistent mood symptoms or diminished energy or libido that affects their quality of life. Although serious adverse effects have not been reported, the long-term safety of DHEA therapy has not been established; we counsel all patients considering DHEA therapy about this lack of long-term data.

  The decision to initiate and continue androgen replacement therapy in such patients should be individualized, as the clinical consequences of androgen deficiency and the response to androgen replacement vary widely across individuals. Females with adrenal insufficiency due to classic congenital adrenal hyperplasia are not candidates for DHEA therapy, as they have elevated rather than low circulating androgen concentrations. (See "Genetics and clinical manifestations of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency".)

- **Males** – In males, androgen replacement therapy is unnecessary; adrenal insufficiency does not result in androgen deficiency in males because the testes are the predominant source of androgens. If males with adrenal insufficiency have persistent symptoms of fatigue, low energy or libido, or reduced quality of life, glucocorticoid and mineralocorticoid (if needed) regimens should be re-evaluated and optimized. If symptoms continue, alternative causes for these symptoms should be investigated.

Approach to a therapeutic trial — For females who opt for a trial of androgen replacement therapy, we typically start DHEA 25 to 50 mg once daily in the morning and adjust the dose based upon the serum DHEA concentration, clinical response, and occurrence of adverse effects. We initiate a treatment trial of three to six months and counsel patients that the therapeutic effects of DHEA may take months to evolve (algorithm 1) [36]. (See 'Androgen therapy monitoring' below.)

- **Assessment of clinical benefit** – Clinical benefits, if they occur, should be evident by six months of therapy. If no clear and enduring clinical benefit is evident after six months of treatment, DHEA therapy is discontinued. If clinical benefit results but androgenic side effects emerge, the DHEA dose should be reduced. DHEA has a long half-life and may be taken every second or third day if daily dosing confers side effects [36]. Common androgenic side effects of DHEA therapy in women include oily skin, hirsutism, acne, and increased sweating and odor [37].

- **Biochemical monitoring** – We measure on-treatment serum DHEAS concentrations in the morning, prior to DHEA administration, and target a value in the middle of the reference range [1]. In most women, DHEA 25 mg daily is sufficient to normalize the serum DHEAS concentration [38]. We avoid DHEA doses higher than 50 mg daily. In females receiving concurrent growth hormone therapy, insulin-like growth factor 1 (IGF-1) concentrations may rise and therefore also should be monitored [39]. Some patients may require a reduction in growth hormone dose when taking DHEA [36].

- **Potential benefits and risks of treatment** – Although studies suggest that DHEA can modestly improve some symptoms in females with adrenal insufficiency, existing evidence does not support the use of therapy in all females with adrenal insufficiency or in males. The best available data on DHEA therapy in females with adrenal insufficiency are from a meta-analysis of 10 trials that found a small improvement in health-related quality of life with DHEA treatment compared with placebo [37]. A small, and perhaps trivial, beneficial effect was evident for depression but not for anxiety or sexual well-being. Nonetheless, clinical trial data are heterogeneous, and individual patients may benefit from therapy [36].

  In the United States, lack of product quality control is a significant limitation to androgen replacement therapy, as DHEA is considered a dietary supplement rather than a hormone preparation. Therefore, DHEA supplements available commercially may not actually contain the advertised dose. This topic is reviewed in detail separately. (See "Overview of herbal medicine and dietary supplements".)

  In a 12-week crossover study in adults with primary and secondary adrenal insufficiency, DHEA treatment (50 mg daily) did not impact metrics of arterial stiffness or endothelial function [40]. Limited data also suggest that DHEA 50 mg daily does not affect insulin resistance, high sensitivity C-reactive protein, physical performance, or body composition [40,41]. DHEA treatment may lead to a small decrement in serum high-density lipoprotein (HDL) cholesterol concentration [42], but this has not been a universal finding and any implications for cardiovascular risk are unknown.

Androgen therapy monitoring — We monitor DHEA therapy through both clinical assessments and measurement of serum DHEA concentrations [1,38]. We perform these assessments every three months during treatment initiation and dose titration and at least once annually in females on stable replacement regimens. Symptom queries should include libido, mood, energy, and general sense of well-being. Patients also should be monitored for evidence of adverse androgenic effects of therapy.

PATIENT EDUCATION AND SAFETY

Patient education — Patient education is a cornerstone of the management of adrenal insufficiency and should include information about the physiology and clinical implications of cortisol deficiency, as well as emergency precautions that all patients should follow (table 4). Patient counseling should be ongoing and reinforced at each clinic visit given the life-threatening nature and complexity of the disease. Patients should be assured that they can lead active and vigorous lives provided they adhere to glucocorticoid replacement therapy and follow the emergency precautions detailed below. The patient and at least one household member or caregiver should be counseled about:

- The nature of the hormonal deficit and the rationale for treatment
- Maintenance medications and adjustment during minor illnesses
- When to consult a clinician
- When and how to inject a glucocorticoid for emergencies

The major risk to patients with adrenal insufficiency is the lack of a normal serum cortisol response to stress. Consequently, patients must receive extensive counseling to anticipate and recognize situations of increased physiologic stress and to modify therapy accordingly. (See 'Circumstances requiring glucocorticoid dose adjustment' below.)

Emergency precautions — Critical emergency precautions include the following:

- Every patient should wear a medical alert (Medic Alert) bracelet or necklace and carry the Emergency Medical Information Card that is supplied with it or a similar medical information card (eg, European Emergency Card). Both the medical alert bracelet and medical information card should indicate the diagnosis, the patient's daily medications and doses, and the clinician to contact in case of emergency.

- Patients should be counseled in detail about "sick day rules," circumstances that require glucocorticoid dose adjustments. These include illness, surgery, and other acute

physiologic stressors. Patients also should be counseled as to when they need to consult a clinician. (See 'Circumstances requiring glucocorticoid dose adjustment' below.)

- Every patient should have injectable glucocorticoid, such as 100 mg vials of hydrocortisone, along with needles and syringes for injection. Patients should assemble injection kits and keep them in a readily accessible place known to all members of the household. If hydrocortisone powder is prescribed, patients need vials of sterile 0.9 percent saline for drug reconstitution. Injectable hydrocortisone is also available in a single-dose vial system that only requires mixing prior to injection. We instruct the patient and one or more household members on how to reconstitute or mix and administer injectable hydrocortisone. Hydrocortisone may be administered either through intramuscular or subcutaneous injection. Subcutaneous injection confers a rapid increase in serum cortisol level, and patients may prefer subcutaneous to intramuscular injection [43].

  Injectable hydrocortisone should be administered if any of the following occur:

  - An injury with substantial blood loss (more than a cup) or fracture
  - Nausea and vomiting with inability to retain oral medications
  - Symptoms of acute cortisol deficiency (eg, severe lightheadedness, nausea and vomiting, or weakness)
  - The patient is found unresponsive or with reduced consciousness

  The entire dose of medication should be injected (100 mg of hydrocortisone), and the patient or household member should seek medical help **immediately** after the injection. We counsel patients to have a low threshold for injecting the hydrocortisone: if it might be necessary, it should be injected, and medical attention should be sought.

Emergency precautions should be reviewed at each clinic visit, including verification that patients have unexpired injectable hydrocortisone.

Circumstances requiring glucocorticoid dose adjustment — Cortisol secretion normally increases with physiologic stressors including illness and surgery. For patients with adrenal insufficiency, such circumstances require transient increases in glucocorticoid doses to prevent adrenal crisis. Few data are available to guide these dose adjustments, which are generally based on stress physiology and clinical experience. Glucocorticoid dose increases are **not** usually needed for psychological stress (eg, anxiety or depression) or moderate exercise.

Acute illness

- **Mild to moderate illness**

  - **Minor illness** – During minor illnesses, such as upper respiratory infections with general symptoms and fever, patients should increase their glucocorticoid dose to two to three times the usual daily dose for three days (known as the three-by-three rule). This can be done without consulting the treating clinician. An increase in glucocorticoid dose is **not** necessary for mild symptoms (eg, congestion) in the absence of fever.

    The hydrocortisone dose adjustment should be implemented immediately upon the onset of symptomatic illness. We counsel patients to double or triple the usual scheduled doses depending on the severity of the illness (table 4). For example, patients who normally take 10 mg of hydrocortisone in the morning and 5 mg in the afternoon can take 20 to 30 mg of hydrocortisone in the morning and 10 to 15 mg in the afternoon for three days. Doses at the higher end of this range (ie, triple the usual dose) are indicated in the setting of fever >101°F or persistent nausea. If emesis occurs, particularly if it prevents retention of oral glucocorticoid, the patient should administer injectable glucocorticoid and immediately seek emergency care. (See 'Emergency precautions' above.)

    The increased dose will decrease fever and malaise and will not compromise the immune response.

  - **Persistent illness** – If the illness worsens during the three days or if the patient cannot resume the usual maintenance dose on the fourth day without symptoms of cortisol deficiency, the individual should contact the treating clinician. Patients with persistent fever or worsening symptoms of illness require in-person evaluation. In individuals with adrenal insufficiency, the threshold for hospitalization should be low. Patients with nausea and vomiting who are unable to retain oral medications should be counseled to administer injectable glucocorticoid therapy and immediately seek emergency medical attention. (See 'Emergency precautions' above.)

  - **Illness requiring hospitalization** – For patients with moderately severe illness (eg, community acquired pneumonia) who require hospitalization but not intensive care, we administer 50 to 75 mg hydrocortisone daily in divided doses (eg, 25 mg every 8 to 12 hours). This may be given orally if the patient is alert and can tolerate oral medications. Once the underlying illness improves, we taper the hydrocortisone dose over two to three days until the usual maintenance dose is resumed. If the patient develops evidence of cortisol deficiency during taper, we resume the lowest dose that alleviated symptoms.

- **Critical illness (major trauma, illness requiring intensive care)** – During critical illness, hydrocortisone 100 mg (intravenous [IV] or intramuscular) and isotonic saline infusion should be administered immediately. This should be followed by hydrocortisone 200 mg daily, delivered either as a continuous infusion or 50 mg IV every six hours, with continuous isotonic fluid administration. Patients also require cardiac monitoring and management of hypoglycemia and electrolyte abnormalities as needed. The hydrocortisone dose is tapered as clinical status improves. (See 'Adrenal crisis' above.)

Surgery — Glucocorticoid dosing during surgery primarily depends on the nature of the surgical procedure (table 4).

- **Minor surgical stress** – For minor surgical procedures such as herniorrhaphy, patients should receive an extra dose of hydrocortisone 25 mg daily (or equivalent) on the day of surgery only with close monitoring. The patient can return to the usual replacement dose the following day if clinical course is uncomplicated [44,45].

- **Moderate surgical stress** – For moderate surgical stress (eg, cholecystectomy, joint replacement), patients should receive divided IV doses equivalent to hydrocortisone 50 to 75 mg daily on the day of surgery and the first postoperative day [44,45]. If the clinical course is uncomplicated, the usual dose may be resumed on the second postoperative day with oral or IV formulations as appropriate.

- **Major surgical stress** – For major surgical procedures (eg, cardiac bypass), patients should receive hydrocortisone 100 mg IV administered prior to the procedure followed by a total daily dose equivalent to hydrocortisone 150 to 200 mg. This should be administered in divided doses (eg, 50 mg IV every six to eight hours) for two to three days perioperatively [44]. If the postoperative course is uncomplicated, a rapid taper (eg, daily dose reduction by 50 percent) to the usual maintenance dose can begin on postoperative day 3 or 4.

- **Postsurgical complications** – If post-surgical complications develop, management of the glucocorticoid taper depends on the severity of the complication. Glucocorticoid dosing should be guided by the severity of illness or stress imparted by the complication. (See 'Acute illness' above.)

Fasting — Patients with adrenal insufficiency are at risk for complications due to fasting, which usually occurs in the setting of religious observances such as Yom Kippur, Ramadan, or Fast Sunday. Glucocorticoid replacement therapy is complicated both by the restriction on taking oral medications during the fasting period and the slightly elevated physiologic stress caused by fasting.

Consistent with published recommendations for management during Ramadan [46], we typically ask patients with adrenal insufficiency on short-acting glucocorticoid regimens to transition to prednisolone 5 mg once daily prior to the fast. During fasting, the prednisolone dose is taken immediately before initiation of the fast (eg, at dawn during Ramadan). This strategy avoids the need for extended dosing intervals with immediate-release hydrocortisone with the attendant risks of hypoglycemia or symptoms of acute cortisol deficiency.

All patients should receive counseling on adequate hydration, sick day rules, when to urgently terminate their fast, and when to administer an emergency injection of glucocorticoid. Patients at high risk for complications should be advised to avoid fasting. Patients with primary adrenal insufficiency can maintain their usual dose of fludrocortisone, also taken once daily prior to initiation of the fast.

Pregnancy and labor

- **Pregnancy**

  - **Glucocorticoid therapy** – For pregnant individuals, we prefer hydrocortisone for glucocorticoid replacement therapy [1]. Hydrocortisone is short-acting, does not require enzymatic activation, and is metabolized by the placenta. It therefore provides the most predictable dosing with lowest risk of glucocorticoid overexposure for the developing fetus. For individuals with adrenal insufficiency who are taking other agents and contemplating pregnancy, we ask them to switch to hydrocortisone and achieve a stable dosing regimen prior to conception.

    - **Early pregnancy (first and second trimester)** – During early pregnancy, the patient's usual glucocorticoid replacement dose is continued with monitoring for evidence of glucocorticoid over- or undertreatment at least once every trimester. (See 'Glucocorticoid therapy monitoring' above.)

      In pregnant individuals, failure to achieve expected weight gain rather than overt weight loss is a sign of undertreatment. Severe fatigue and postural hypotension also suggest undertreatment, whereas hypertension and hyperglycemia may indicate overtreatment, particularly when present during early pregnancy.

    - **Late pregnancy (third trimester)** – In the third trimester, most patients require an increase in the hydrocortisone dose of approximately 20 to 40 percent (eg, 2.5 to 10 mg daily) [3]. This adjustment can be made empirically at pregnancy weeks 20 to 24 or as needed on the basis of clinical course [34,47-49]. Most patients

require this increased dose of hydrocortisone due to the progressive rise in corticosteroid-binding globulin (CBG) particularly evident in late pregnancy.

- **Severe nausea and vomiting** – In patients with severe nausea and vomiting in the first trimester who are unable to tolerate oral medications, intramuscular dexamethasone at a dose slightly above physiologic replacement (eg, 1 mg daily) may be used. Dexamethasone should be reserved for intractable vomiting and used for the shortest duration possible. Its use is usually contraindicated during pregnancy as it is not inactivated by placental 11-beta-hydroxysteroid dehydrogenase type 2 and can lead to excess glucocorticoid exposure for the developing fetus.

- **Mineralocorticoid therapy** – Dose adjustments for mineralocorticoid therapy are generally not needed during pregnancy, but serum electrolytes and signs of volume depletion should be monitored at each prenatal visit. If the reference range for pregnant individuals is used, plasma renin activity (PRA) may provide an additional index of adequate fludrocortisone replacement. A PRA in the upper half of the reference range for pregnant individuals is a reasonable target. A PRA suppressed to values less than those in pregnant individuals without adrenal insufficiency (ie, <20 to 25 ng/mL per hour supine or standing) is an indication of overtreatment [50-52].

  The regulation of plasma volume during pregnancy is complex, with upregulation of both aldosterone and the offsetting natriuretic actions of progesterone. Secondary hyperaldosteronism is normal [53], with increased PRA and serum aldosterone concentrations [50,51]. Serum concentrations of progesterone, which competes with aldosterone for binding to the mineralocorticoid receptor in the kidney, are increased throughout pregnancy [54,55]. PRA and serum aldosterone concentrations peak late in the third trimester [50].

- **Labor and delivery** – At the onset of labor, glucocorticoid therapy should be administered as for major surgical stress. This consists of 100 mg hydrocortisone administered at the start of labor followed by 150 to 200 mg daily administered in divided doses every six to eight hours (eg, 50 mg every six hours). After uncomplicated delivery, the hydrocortisone dose may be reduced to double the patient's predelivery dose for one to two days followed by rapid taper to the patient's prepregnancy dose over the following one to two days [49].

- **Clinical outcomes** – If recognized and treated appropriately, adrenal insufficiency rarely leads to pregnancy complications [47]. Before glucocorticoid replacement therapy became

available, pregnancy in women with primary adrenal insufficiency was associated with a maternal mortality rate as high as 35 to 45 percent, and impaired fetal growth was common [56-58]. Most females adequately treated for adrenal insufficiency now go through pregnancy, labor, and delivery without difficulty, and neonates have a normal birth weight.

PROGNOSIS

The prognosis for patients with adrenal insufficiency was poor before the availability of glucocorticoids, with more than 80 percent of patients dying within two years after diagnosis [59]. After glucocorticoids became available for treatment, subsequent reports suggested that patients with autoimmune adrenal insufficiency should have a normal lifespan and can lead fully active lives, including vigorous exercise [48,59]. By contrast, a study based on the Swedish death registry found that patients with adrenal insufficiency have a twofold higher mortality rate than the background population [60]. The reasons for this discrepancy are not understood, and further studies are needed to evaluate whether these patients have premature mortality.

Some studies report significantly reduced subjective quality of life and increased rates of work disability in patients with adrenal insufficiency [61-63]. A Norwegian study of 79 patients who answered a postal survey showed impaired general health and vitality perception and an increase in reported fatigue. Working disability at ages 18 to 67 years was 26 percent, compared with 10 percent in the corresponding general Norwegian population [61]. A German study reported increased depression scores and reduced quality-of-life scores in 210 patients, 18.3 percent of whom did not work because of disability [62]. Improved therapies that better mimic the normal diurnal pattern of cortisol production may help improve quality-of-life outcomes for individuals with adrenal insufficiency.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Adrenal insufficiency".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Addison disease (The Basics)" and "Patient education: Adrenal crisis (The Basics)")
- Beyond the Basics topics (see "Patient education: Adrenal insufficiency (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Adrenal crisis** – Adrenal crisis is a life-threatening emergency that requires immediate treatment (table 1). Treatment must be initiated promptly for all patients with suspected adrenal crisis and should never be delayed for diagnostic testing. The precipitating cause of adrenal crisis should be identified and treated appropriately. (See 'Adrenal crisis' above and 'Emergency management' above.)
  - **Glucocorticoid treatment** – Parenteral glucocorticoid therapy is required for acute adrenal crisis. We suggest hydrocortisone rather than other glucocorticoids (**Grade 2C**). We administer hydrocortisone as a 100 mg intravenous (IV) bolus followed by 50 mg IV every six hours (or 200 mg/24 hours as a continuous IV infusion) for the first 24 hours. If hydrocortisone is unavailable, alternatives include methylprednisolone 40 mg IV and dexamethasone 4 to 6 mg IV (table 1 and table 2). However, since these agents have less mineralocorticoid activity than hydrocortisone, fludrocortisone may also be needed in patients with known or suspected primary adrenal insufficiency. If hydrocortisone is given, mineralocorticoid replacement is not needed in the acute setting. (See 'Emergency management' above.)
  - **Fluid and electrolytes** – Patients with adrenal crisis require fluid resuscitation. We administer isotonic fluid, typically saline (eg, 0.9 percent saline solution or 5 percent dextrose in 0.9 percent saline), to correct hypovolemia and hyponatremia. Dextrose-containing fluids help correct confirmed or suspected hypoglycemia. We begin with

rapid infusion of 1 L over the first hour and typically give at least 2 to 3 L within the first 24 hours. We monitor serum electrolyte and glucose levels closely. (See 'Emergency management' above.)

- **Subsequent treatment and monitoring** – Hypotension, hyponatremia, or hyperkalemia that is refractory to parenteral hydrocortisone and isotonic fluid administration suggests an etiology other than adrenal crisis. Once the patient has stabilized, we taper hydrocortisone over one to three days and convert to an oral stress dose or maintenance regimen once the patient can take oral medications. Unless cortisol deficiency is excluded, we continue maintenance glucocorticoid replacement until the patient undergoes outpatient evaluation. For patients with known or suspected primary adrenal insufficiency, we begin fludrocortisone therapy when the hydrocortisone dose is tapered below 40 mg daily. (See 'Subsequent management' above and "Diagnosis of adrenal insufficiency in adults", section on 'Suspected adrenal crisis'.)

- **Chronic adrenal insufficiency**

  - **Glucocorticoid replacement** – All individuals with adrenal insufficiency require glucocorticoid replacement therapy. We use the lowest glucocorticoid dose that relieves symptoms of glucocorticoid deficiency (algorithm 1).

    - **Preferred therapy with hydrocortisone** – In patients with chronic adrenal insufficiency, we suggest replacement with hydrocortisone therapy rather than other glucocorticoids (**Grade 2C**). Hydrocortisone is typically administered in two or three daily divided doses (total daily dose of 15 to 25 mg). These regimens can be adjusted to provide variable glucocorticoid exposure over the course of a day and better replicate the normal circadian pattern of endogenous cortisol secretion. The short-acting agent cortisone acetate (20 to 35 mg daily in two or three divided doses) is a reasonable alternative, but dosing may be less predictable due to the need for enzymatic activation. (See 'Hydrocortisone (preferred glucocorticoid)' above.)

    - **Adherence challenges or persistent symptoms** – In individuals who have persistent symptoms or difficulty adhering to multiple daily glucocorticoid doses, the longer-acting agent prednisolone may be used. Longer-acting glucocorticoids may confer higher risk of overtreatment. (See 'Alternative regimens' above.)

  - **Mineralocorticoid replacement in patients with primary adrenal insufficiency** – Virtually all patients with primary adrenal insufficiency require mineralocorticoid

replacement therapy, whereas mineralocorticoid replacement is rarely needed in patients with central adrenal insufficiency. In patients with confirmed mineralocorticoid deficiency, we initiate fludrocortisone 0.05 to 0.1 mg daily. We adjust the fludrocortisone dose to lower the plasma renin activity to the upper normal range. (See 'Mineralocorticoid replacement for selected individuals' above.)

- **Androgen replacement in selected females** – For females with persistent symptoms of low mood, diminished energy or libido, or reduced quality of life despite optimization of other hormone replacement therapy, we suggest a trial of dehydroepiandrosterone (DHEA) therapy (**Grade 2C**). We initiate therapy with DHEA 25 to 50 mg daily and monitor for clinical benefit. DHEA therapy should not be used in males, in whom adrenal insufficiency does not lead to androgen deficiency. (See 'Androgen replacement therapy for selected females' above.)

- **Patient safety** – Cortisol deficiency can be life-threatening, so continual patient education and counseling are essential facets of management for all patients with chronic adrenal insufficiency. All patients should wear a medical alert bracelet and have emergency glucocorticoid injection kits. (See 'Patient education and safety' above.)

- **Circumstances requiring glucocorticoid dose adjustment** – The glucocorticoid dose must be increased during illness, surgery, and other physiological stressors (table 4). The extent and duration of the dose increase depends on the severity of the stressor. Pregnant individuals require close monitoring to assess the adequacy of both glucocorticoid and mineralocorticoid regimens. (See 'Circumstances requiring glucocorticoid dose adjustment' above.)

ACKNOWLEDGMENT

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Topic 155 Version 30.0

GRAPHICS

Treatment of acute adrenal insufficiency (adrenal crisis) in adults

Emergency measures

1. Establish intravenous access with a large-gauge needle.
2. Draw blood for immediate serum creatinine, BUN, electrolytes, glucose, and routine measurement of plasma cortisol and ACTH. Do not wait for laboratory results.
3. Infuse 1 liter of isotonic saline or 5% dextrose in isotonic saline as quickly as possible. Repeat fluid bolus as needed for volume resuscitation, followed by maintenance fluids. Frequent hemodynamic monitoring and measurement of serum electrolytes should be performed to avoid iatrogenic fluid overload.
4. Give hydrocortisone (100 mg intravenous bolus), followed by 50 mg intravenously every 6 hours (or 200 mg/24 hours as a continuous intravenous infusion for the first 24 hours). If hydrocortisone is unavailable, alternatives include methylprednisolone and dexamethasone. Saline must be administered if dexamethasone is given instead of hydrocortisone.
5. Use supportive measures as needed.*

Subacute measures after stabilization of the patient

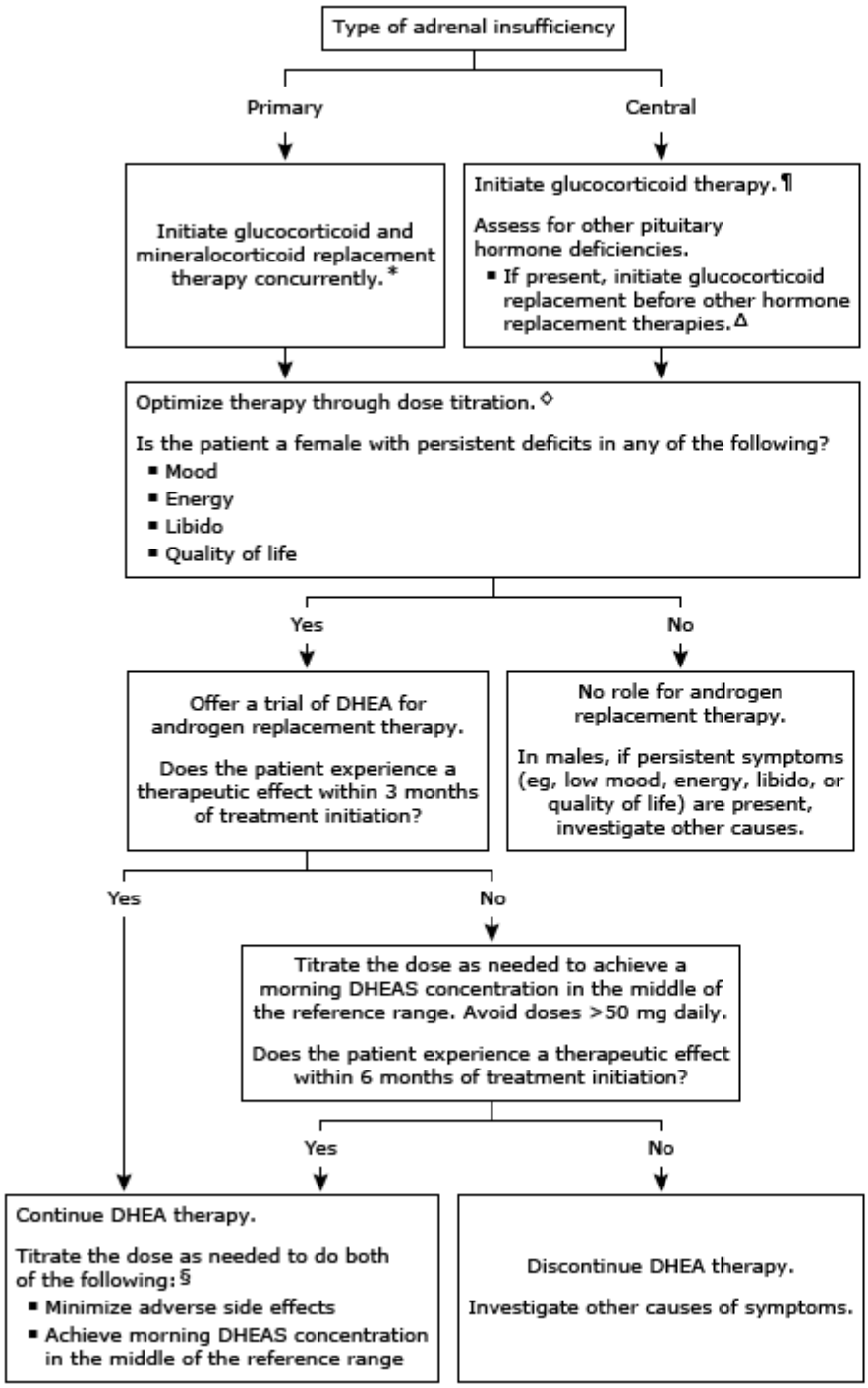
1. Continue intravenous isotonic saline at a slower rate for next 24 to 48 hours.
2. Search for and treat possible infectious precipitating causes of the adrenal crisis.
3. Taper parenteral glucocorticoid over 1 to 3 days, if precipitating or complicating illness permits, to oral glucocorticoid maintenance dose.
4. For patients with primary adrenal insufficiency, begin mineralocorticoid replacement with fludrocortisone, 0.1 mg by mouth daily, when saline infusion is stopped or hydrocortisone dose is tapered to <40 mg daily.
5. If the patient does not have known adrenal insufficiency, confirm the diagnosis and determine the underlying cause. Refer to UpToDate topics on the diagnostic and etiologic evaluation of adrenal insufficiency in adults.

BUN: blood urea nitrogen; ACTH: corticotropin.

* Electrolyte abnormalities may include hyponatremia, hyperkalemia, or rarely hypercalcemia. Hyponatremia is rapidly corrected by cortisol and volume repletion.

Graphic 67329 Version 10.0

Adrenal hormone replacement therapy in adults with adrenal insufficiency



Typical adrenal hormone replacemer regimens for chronic adrenal insuffic in adults

Glucocorticoid therapy (all patients)¥

Preferred replacement therapy:
- Hydrocortisone 15 to 25 mg orally daily, divided in 2 or 3 decreasing doses

Alternative therapy:
- Cortisone acetate 20 to 35 mg orally daily, divided in 2 or 3 decreasing doses
- Prednisolone 3 to 5 mg orally daily (once daily or divided in 2 doses)

Emergency therapy: In addition to a daily replac regimen, all patients should be counseled in deta circumstances that require dose adjustment (ie, "sick day rules") and must be provided with glucocorticoid (eg, 100 mg vial of hydrocortisone in case of emergency. Refer to UpToDate topic fo

Mineralocorticoid replacement therapy (primary adrenal insufficiency)

Fludrocortisone 0.05 to 0.1 mg orally once daily

Androgen replacement therapy (females with persistent symptoms)

DHEA 25 to 50 mg orally once daily

This algorithm summarizes our suggested approach to adrenal hormone replacement in adults with chronic adrenal insufficiency. To minimize adverse effects, all doses should be individualized to provide the lowest dose that relieves symptoms. Dose adjustments may be required for drug interactions. When initiating or changing drug therapy, use of a drug interactions database, such as the drug interaction program, is advised. This algorithm is intended for use with additional UpToDate content. For additional details, including the evidence supporting this approach, refer to UpToDate topics on the treatment of chronic adrenal insufficiency in adults.

DHEA: dehydroepiandrosterone; DHEAS: dehydroepiandrosterone sulfate.

* Aldosterone and renin levels should be measured prior to initiating mineralocorticoid replacement therapy as rare patients with primary adrenal insufficiency can have mild mineralocorticoid deficiency that does not require treatment.

¶ In central (ie, secondary or tertiary) adrenal insufficiency, mineralocorticoid replacement is not needed at the time of diagnosis. In rare patients with longstanding disease, mineralocorticoid replacement may become necessary.

Δ Initiation of thyroid or growth hormone replacement before glucocorticoid replacement can precipitate adrenal crisis.

◇ Glucocorticoid replacement regimens are titrated on the basis of clinical signs and symptoms of inadequate (eg, fatigue, nausea, weight loss, weakness, hypotension) or excessive (eg, weight gain, edema, hypertension) glucocorticoid exposure. The adequacy of mineralocorticoid replacement is determined by both clinical and biochemical assessments and requires routine measurement of serum potassium, sodium, and creatinine levels and plasma renin activity. Monitoring and optimization of glucocorticoid and mineralocorticoid regimens are reviewed in detail in other UpToDate content.

§ The principal signs of excessive androgen replacement include hirsutism, sweating, odor, oily skin, and acne. DHEA has a long half-life and may be taken every second or third day if needed to minimize side effects. Some females have therapeutic benefit with DHEAS levels below the middle of the reference range, but higher levels should be avoided. The DHEA dose should not exceed 50 mg daily. DHEA is available in the United States and some other countries as a nonprescription dietary supplement, and these products are not well regulated for potency or purity.

¥ To mimic endogenous cortisol production, short-acting glucocorticoid regimens are given in decreasing, divided doses throughout the day, and the last dose is given no later than 4 to 6 hours before bedtime. For example, in a typical twice-daily regimen with hydrocortisone or cortisone acetate, approximately two-thirds of the total daily dose is taken in the morning and one-third in the afternoon. When prednisolone is taken in divided doses, approximately 70 to 80% of the total daily dose is taken in the morning and the remainder at bedtime.

Graphic 142464 Version 6.0

Comparison of systemic glucocorticoid preparations

	Equivalent doses (mg)	Antiinflammatory activity relative to hydrocortisone*	Duration of action (hours)
Glucocorticoids			
Short acting			
Hydrocortisone (cortisol)	20	1	8 to 12
Cortisone acetate	25	0.8	8 to 12
Intermediate acting			
Prednisone	5	4	12 to 36
Prednisolone	5	4	12 to 36
Methylprednisolone	4	5	12 to 36
Triamcinolone	4	5	12 to 36
Long acting			
Dexamethasone	0.75	30	36 to 72
Betamethasone	0.6	30	36 to 72
Mineralocorticoids			
Fludrocortisone	Not used for an antiinflammatory effect¶. The typical dose of fludrocortisone for mineralocorticoid replacement is 0.1 to 0.2 mg.		12 to 36

The mineralocorticoid effect of commonly administered glucocorticoids may be estimated as follows:

- When given at replacement doses, triamcinolone, dexamethasone, and betamethasone have no clinically important mineralocorticoid activity.
- 20 mg hydrocortisone and 25 mg of cortisone acetate each provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg fludrocortisone.
- Prednisone or prednisolone given at antiinflammatory doses ≥50 mg per day provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg of fludrocortisone.

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* Equivalent antiinflammatory dose shown is for oral or intravenous (IV) administration. Relative potency for intraarticular or intramuscular administration may vary considerably.

¶ The antiinflammatory potency is 10 to 15 times that of hydrocortisone; however, fludrocortisone is not used clinically as an antiinflammatory agent.

Data from:

1. *Schimmer BP, Funder JW. ACTH, adrenal steroids, and pharmacology of the adrenal cortex. In: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12th ed, Brunton LL, Chabner BA, Knollmann BC (Eds), McGraw-Hill Education 2011.*
2. *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, 9:30.*

Graphic 64138 Version 23.0

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
▪ Adagrasib ▪ Atazanavir ▪ Ceritinib ▪ Clarithromycin ▪ Cobicistat and cobicistat-containing coformulations ▪ Darunavir ▪ Idelalisib ▪ Indinavir ▪ Itraconazole ▪ Ketoconazole ▪ Levoketoconazole ▪ Lonafarnib ▪ Lopinavir ▪ Mifepristone[*] ▪ Nefazodone ▪ Nelfinavir ▪ Nirmatrelvir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir plus dasabuvir ▪ Posaconazole ▪ Ritonavir and ritonavir-containing coformulations ▪ Saquinavir ▪ Tucatinib ▪ Voriconazole	▪ Amiodarone[¶] ▪ Aprepitant ▪ Berotralstat ▪ Cimetidine[¶] ▪ Conivaptan ▪ Crizotinib ▪ Cyclosporine[¶] ▪ Diltiazem ▪ Duvelisib ▪ Dronedarone ▪ Erythromycin ▪ Fedratinib ▪ Fluconazole ▪ Fosamprenavir ▪ Fosaprepitant[¶] ▪ Fosnetupitant-palonosetron ▪ Grapefruit juice ▪ Imatinib ▪ Isavuconazole (isavuconazonium sulfate) ▪ Lefamulin ▪ Letermovir ▪ Netupitant ▪ Nilotinib ▪ Ribociclib ▪ Schisandra ▪ Verapamil	▪ Apalutamide ▪ Carbamazepine ▪ Encorafenib ▪ Enzalutamide ▪ Fosphenytoin ▪ Lumacaftor ▪ Lumacaftor-ivacaftor ▪ Mitotane ▪ Phenobarbital ▪ Phenytoin ▪ Primidone ▪ Rifampin (rifampicin)	▪ Bexarotene ▪ Bosentan ▪ Cenobamate ▪ Dabrafenib ▪ Dexamethasone[Δ] ▪ Dipyrone ▪ Efavirenz ▪ Elagolix, estradiol, and norethindrone therapy pack[◇] ▪ Eslicarbazepine ▪ Etravirine ▪ Lorlatinib ▪ Mitapivat ▪ Modafinil ▪ Nafcillin ▪ Pexidartinib ▪ Repotrectinib ▪ Rifabutin ▪ Rifapentine ▪ Sotorasib ▪ St. John's wort

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.
- These classifications are based upon US Food and Drug Administration (FDA) guidance.[1,2] Other sources may use a different classification system resulting in some agents being classified differently.

- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (eg, target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

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* Mifepristone is a significant inhibitor of CYP3A4 when used chronically (eg, for hyperglycemia in patients with Cushing syndrome); not in single-dose use.

¶ Classified as a weak inhibitor of CYP3A4 according to FDA system.[1]

Δ Classified as a weak inducer of CYP3A4 according to FDA system.[1]

◇ The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

References:

1. *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry (January 2020) available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions.*
2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*

Graphic 76992 Version 98.0

Patient education and safety measures for adults with chronic adrenal insufficiency

1. Patient education
Educate patient about the disease, how to manage minor illnesses and major stressors, and how to inject hydrocortisone or other glucocorticoid intramuscularly or subcutaneously.
Refer to UpToDate patient education topics on adrenal insufficiency (Addison disease).
2. Emergency precautions
Obtain medical alert bracelet/necklace, Emergency Medical Information Card, and injectable glucocorticoid (eg, hydrocortisone 100 mg).
3. Treatment of minor febrile illness or surgical stress
Increase glucocorticoid dose 2- to 3-fold for the few days of illness. Do not change mineralocorticoid dose.
Patient is instructed to contact clinician if illness worsens or persists for more than 3 days.
No extra supplementation is needed for most uncomplicated, outpatient dental procedures under local anesthesia.
Glucocorticoid dosing for surgical stress: ▪ Minor (eg, herniorrhaphy) – An extra dose of hydrocortisone 25 mg IV (or equivalent) on day of procedure ▪ Moderate (eg, orthopedic surgery) – Hydrocortisone 50 to 75 mg IV (or equivalent) on day of surgery and postoperative day 1 ▪ Major (eg, cardiac bypass) – Hydrocortisone 100 mg IV prior to the procedure and 150 to 200 mg IV (or equivalent) in 3 or 4 divided doses on day of surgery and postoperative days 1 and 2 Then return to usual daily glucocorticoid dose if postoperative course is uncomplicated.
General anesthesia or IV sedation should not be performed in the office setting.
4. Emergency treatment of severe stress or trauma
Each patient should have an injectable glucocorticoid (eg, 100 mg vials of hydrocortisone), needles and syringes for injection, and vials of sterile 0.9% normal saline (if needed for reconstitution).
Instruct patient/caregivers on how to reconstitute the vial and to inject entire dose intramuscularly or subcutaneously in event of severe stress or trauma. Patient should seek medical help immediately after injection.

IV: intravenously.

Courtesy of Lynette Nieman, MD.

Additional data from:

1. *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; 101:364.*

Graphic 78904 Version 5.0