INTRODUCTION — Primary adrenal insufficiency (Addison's disease) is due to adrenocortical disease, while secondary and tertiary adrenal insufficiency are due to disorders of the pituitary gland (ACTH secretion) or the hypothalamus (corticotropic-releasing hormone secretion), respectively. Primary adrenal insufficiency is associated with both cortisol and mineralocorticoid deficiency. In contrast, secondary and tertiary adrenal insufficiency are associated with cortisol, 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 all forms of 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's disease)" and see "Clinical manifestations of adrenal insufficiency in adults" and see "Diagnosis of adrenal insufficiency in adults").

ADRENAL CRISIS — The major clinical feature of acute adrenal insufficiency (adrenal crisis) is volume depletion and hypotension, usually resulting from mineralocorticoid deficiency. While isolated glucocorticoid deficiency does not lead to volume depletion, it decreases vascular tone, which contributes further to hypotension. Thus, adrenal crisis occurs less frequently in patients with secondary or tertiary adrenal insufficiency. (See "Clinical manifestations of adrenal insufficiency in adults").

However, patients with central causes of adrenal insufficiency also may present with adrenal crisis during acute stress, or with acute cortisol deficiency due to pituitary infarction or after surgical cure of Cushing's syndrome. (See "Clinical manifestations of adrenal insufficiency in adults".
section on Pituitary apoplexy). Adrenal crisis may also occur in patients who are abruptly withdrawn from exogenous glucocorticoids.

Biochemical features of adrenal crisis include hyperkalemia (in patients with mineralocorticoid deficiency) and hyponatremia. Hyponatremia occurs because of mineralocorticoid deficiency and also due to inappropriate secretion of antidiuretic hormone (vasopressin) that is caused by cortisol (not aldosterone) deficiency. In patients with primary adrenal deficiency, combined mineralocorticoid and glucocorticoid deficiency lead to urinary sodium loss, plasma volume depletion with increased serum urea, patients with pure cortisol deficiency have slightly increased blood volume, dilutional hyponatremia, and less urinary sodium loss. (See "Hyponatremia and hyperkalemia in adrenal insufficiency").

Management — Adrenal crisis is a life-threatening emergency that requires immediate treatment (show table 1).

- Treatment of patients who present in possible adrenal crisis should not be delayed while diagnostic tests are performed. Blood for serum cortisol, renin, ACTH and serum chemistry should be drawn and therapy initiated immediately. The serum chemistry results guide initial treatment; the hormone values return later and are used to confirm the diagnosis (cortisol) or evaluate the differential diagnosis (ACTH and renin).

- 1 to 3 liters of 0.9 percent saline solution or 5 percent dextrose in 0.9 percent saline (to correct possible hypoglycemia) should be infused intravenously within the first 12 to 24 hours based on assessment of volume status and urine output.

- Hypotonic saline should not be used because it can worsen the hyponatremia.

Glucocorticoids — In a patient without a previous diagnosis of adrenal insufficiency, dexamethasone [4 mg intravenous bolus] is preferred because, in contrast to hydrocortisone, it is not measured in serum cortisol assays [1].

For patients with a known diagnosis of adrenal insufficiency who present with adrenal crisis, dexamethasone [4 mg iv bolus], hydrocortisone 100 mg IV bolus, or any intravenous glucocorticoid preparation, may be used. (show table 2). This can rapidly decrease the inappropriate vasopressin production with increased clearance of free water and correction of hyponatremia.

- In contrast to glucocorticoid replacement, mineralocorticoid replacement is not useful acutely because it takes several days for its sodium-retaining effects to appear, and adequate sodium replacement can be achieved by intravenous saline alone. However, in patients with
known primary adrenal insufficiency with potassium >6.0 mEq/L, hydrocortisone is preferred because of its mineralocorticoid activity.

- Unless there is a major complicating illness, parenteral glucocorticoid therapy can be tapered over one to three days and changed to an oral maintenance dose.

Diagnostic tests — After initial treatment, the precipitating cause of the adrenal crisis (as an example, bacterial infection, viral gastroenteritis) should be sought and appropriately treated.

Once the patient's condition is stable, the diagnosis can be confirmed in patients not known to have adrenal insufficiency with a short ACTH stimulation test. This should be followed by tests to determine the cause of the adrenal insufficiency. (See "Diagnosis of adrenal insufficiency in adults").

LONGTERM MANAGEMENT — One of the important components of therapy in chronic adrenal insufficiency is patient education (show table 3). The patients should be told that they can lead an active and vigorous life as long as they take replacement therapy and follow a few common-sense precautions. The patient and responsible family members should be instructed about:

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

Glucocorticoid regimens — The ideal glucocorticoid replacement therapy would:

- mimic the endogenous cortisol rhythm, with a nadir at bedtime and peak values in the early morning before waking.
- have little inter-individual variability in metabolism, so that the correct dose could be predicted.
- be amenable to easy dose-titration.
- be easily monitored.
- have few adverse effects.

Unfortunately, there are no head-to-head comparisons of various glucocorticoid replacement regimens. Various regimens have been advocated, using short-acting (cortisone acetate or hydrocortisone) or long-acting (prednisone/prednisolone, dexamethasone) agents. (show table 2).

Short-acting regimens — Short-acting regimens roughly mimic the normal diurnal rhythm.
The bioavailability of hydrocortisone is nearly 100 percent, and serum cortisol concentrations rise rapidly in the 30 minutes or so after ingestion. However, after a large dose, the corticosteroid-binding globulin (CBG) capacity for cortisol is exceeded at about 25 mcg/dL. As a result, the serum free cortisol increases, and is rapidly filtered into the urine, resulting in a rapid decline in serum total cortisol concentrations to 25 µg/dL (690 nmol/L), after which the decline slows (average plasma half-life about 95 minutes). One study found elevated UFC for 24 hours after a single 25 mg hydrocortisone dose, but to decrease to the normal range, when the 25 mg daily dose was given in five 5 mg doses.

To become biologically active, cortisone must undergo hepatic conversion to cortisol. It is either largely unabsorbed or not metabolized after intramuscular administration. Because of these shortcomings, hydrocortisone is generally considered to be the better choice for a short-acting glucocorticoid regimen.

In general, the replacement dose of glucocorticoid is aimed at replacing the missing cortisol or its equivalent. The average daily secretion rate of cortisol in normal subjects is 2.7 to 14 mg/M2/day, and the range of replacement doses is wider due to interindividual variation in metabolism of the steroids and the fact that a single dose is less effective than the same amount of steroid administered in multiple doses.

Because of its short half-life, the total daily dose of hydrocortisone is divided into two or three doses. Thrice daily administration mimics the day-curve of cortisol seen in healthy volunteers. A typical twice-daily regimen consists of taking about two-thirds of the total dose upon arising in the morning and one-third in the afternoon to simulate the normal cortisol circadian rhythm. Three times daily regimens use decreasing doses in the morning, early afternoon and late afternoon/early evening (e.g., 10-5-2.5 mg). Most regimens avoid evening doses, because normal subjects secrete little cortisol from about 6 PM to 3 AM.

The authors recommend a variety of replacement doses, including 5 mg/M2 given thrice daily, 10 mg morning and 5 mg in the afternoon, 20 mg total dose, and 15 to 25 mg daily given in two or three divided doses. Hydrocortisone has some mineralocorticoid activity, so fludrocortisone replacement must be decreased appropriately.

While some patients do well on single dose administration, we recommend that a split dose be used when initiating therapy, and that a single dose be used only if patients are not compliant. In one small study, quality of life and patient preference were greatest during three weeks with a split dose regimen (20 mg at 0700h and 10 mg at 1900h) rather than a single total dose in the morning or evening. There are no studies comparing quality of life
of two vs three dose regimens.

Advantages of hydrocortisone include the potential for fine dose adjustments using various tablet strengths. Additionally, one study found that smaller fractionated doses of hydrocortisone (10 mg twice daily) avoided increased intraocular pressure found with a higher dose (20 mg and 10 mg split dose) [12].

A disadvantage of hydrocortisone therapy is the fact that a normal diurnal rhythm cannot be truly replicated: at the time of the morning dose, endogenous serum cortisol concentrations would normally already be at or after the circadian peak. This transient early morning adrenal insufficiency probably accounts for the symptoms of fatigue, lassitude, mild nausea, or headache that are often present upon awakening and that are relieved within 30 to 60 minutes after taking the morning dose of hydrocortisone. Some patients find it helpful to take their initial dose of hydrocortisone in the early morning and go back to sleep for a few hours.

Long-acting glucocorticoid regimens — Longer-acting agents such as dexamethasone or prednisone provide a smoother physiological effect and avoid the marked changes in serum glucocorticoid levels that occur with short-acting drugs. It is not known if this is clinically important. The usual oral daily replacement dosages are 0.5 mg and 5 mg for dexamethasone and prednisone, respectively. Some patients require 2.5 or 7.5 mg for prednisone or 0.25 or 0.75 mg for dexamethasone. (show table 2).

Long-acting agents may be useful in patients who are non-compliant with multiple daily dose schedules, or in those with severe late-evening or early morning symptoms that are not ameliorated by three-times daily hydrocortisone. Disadvantages of long-acting agents include the variable inter-individual metabolism of dexamethasone, and as a result, an inability to predict the correct dose. As a result, patients may be over-treated.

Obese patients and those who metabolize glucocorticoids more rapidly than average may need higher doses; children or small adults and patients who metabolize glucocorticoids less rapidly than average may need lower doses. The dexamethasone dose may need to be increased in patients taking drugs that accelerate hepatic steroid metabolism, such as phenytoin, barbiturates, rifampin, and mitotane [13-16].

Monitoring dose — We suggest using the lowest glucocorticoid dose that relieves symptoms of glucocorticoid deficiency and avoids signs and symptoms of glucocorticoid excess.

- The dose may be too low if symptoms of apparent glucocorticoid deficiency are present. If, however, increasing the dose does not promptly relieve the symptoms, then they have other causes and the
lower steroid dosage should be resumed.

- The dose may be too high if excessive weight gain, facial plethora or other symptoms or signs of Cushing's syndrome, are present.

- Osteoporosis is more likely with excessive glucocorticoid therapy [17]. Increased bone loss in women, but not men, with treated primary adrenal insufficiency was reported in one study [18] and in men but not women in another [19]. Comparison of bone loss in patients treated with daily hydrocortisone 30 mg or prednisone 7.5 mg (doses that are higher than the recommended maintenance doses), found no difference in one study, but lower bone mineral density with prednisone in another [20,21].

A study of 31 patients receiving three different regimens in random order suggested that morning dexamethasone 0.1 mg/15 kg body weight had adverse effects on serum markers of bone turnover as compared with hydrocortisone 10 mg/5 mg or 10/5/5 mg split doses [22]. Although this issue remains unresolved, it does highlight the importance of avoiding excessive doses of glucocorticoid, and may suggest that long-acting glucocorticoids are more likely to reduce bone mineral density. (See "Glucocorticoids and osteoporosis: Pathogenesis and clinical features").

- A low normal or suppressed morning plasma ACTH concentration indicates excessive glucocorticoid replacement in patients with primary adrenal insufficiency. The early morning adrenal insufficiency with hydrocortisone results in plasma ACTH concentrations that are two to eight times higher than normal for several hours in the early morning and for several hours after the cortisol is taken [23-25]. ACTH levels were significantly lower compared to conventional oral therapy, but remained about two-fold elevated in two patients receiving hydrocortisone infusion [25]. Measurements of plasma ACTH are not helpful in patients with secondary insufficiency, in whom levels are expected to be low.

- While some advocate use of normative day-curve cortisol values to assess the adequacy of hydrocortisone therapy [7], other reports suggest that clinical assessment alone works equally well [26].

**Mineralocorticoid replacement**—Most patients with primary adrenal insufficiency eventually require mineralocorticoid replacement to prevent sodium loss, intravascular volume depletion, and hyperkalemia. (Rare patients are sufficiently replaced with hydrocortisone alone and become hypertensive, hypokalemic with even 0.05 mg fludrocortisone twice a week.)

Fludrocortisone (9-alpha-fluorohydrocortisone), a potent synthetic
mineralocorticoid, is given orally in a usual dose of 0.1 mg/day. A lower dose (such as 0.05 mg/day) may be sufficient in patients receiving hydrocortisone, which has some mineralocorticoid activity. However, many patients receiving prednisone or dexamethasone require up to 0.2 mg/day of fludrocortisone to lower their plasma renin activity to the upper normal range [27,28]. (See "Monitoring" below).

The mineralocorticoid dose may have to be increased in the summer, when salt loss in perspiration increases, especially if the patient is routinely exposed to temperatures above about 29ºC (85ºF). Salt intake should be liberal, especially when exercising.

Essential hypertension in patients with primary adrenal insufficiency should be treated by dietary sodium restriction and a lower dose of fludrocortisone [29,30]. Mineralocorticoid therapy usually cannot be discontinued without risking sodium depletion. If an antihypertensive drug is needed, diuretic drugs and spironolactone should not be used, since they simply counteract the action of fludrocortisone.

- Mineralocorticoid replacement is rarely required in patients with secondary adrenal insufficiency, because ACTH is not an important regulator of aldosterone release.

**Monitoring** — The adequacy of mineralocorticoid replacement should be monitored by asking about symptoms of postural hypotension and measuring supine and upright blood pressure and pulse, serum potassium, and plasma renin activity (PRA). Hypertension, edema, and hypokalemia are signs of excessive mineralocorticoid replacement [29].

We suggest adjusting the fludrocortisone dose to lower the PRA to the upper normal range [27,28]. Normal, morning plasma renin activity for seated subjects ranges from about 1 to 4 ng/mL per h (0.8 to 3.0 nmol/L per h). (See "Assays of the renin-angiotensin-aldosterone system in adrenal disease" section on Plasma renin activity).

It is useful to measure PRA annually in all patients and in:

- Newly diagnosed patients, until they are on a stable dose of mineralocorticoids.

- Patients with symptoms consistent with mineralocorticoid deficiency such as salt craving and intermittent mild nausea who have otherwise normal findings on physical examination.

In asymptomatic patients with normal serum electrolyte concentrations but high PRA, the fludrocortisone dose should not be raised to normalize PRA. Although one might predict that this would be a physiologic dose (normal PRA in an asymptomatic, normokalemic patient), patients may develop
hypokalemia and edema [31]. (See "Clinical features of primary aldosteronism").

**Androgen replacement** — In women, the adrenal cortex is the primary source of androgen in the form of dehydroepiandrosterone and dehydroepiandrosterone sulfate. The physiological role of these androgens in women and men is not known.

- Clinical trial data suggest that in women with primary adrenal insufficiency, replacement with 50 mg of DHEA daily may be beneficial for outcomes such as mood and psychological well-being. Androgenic side effects, such as acne, are common. (See "Dehydroepiandrosterone and its sulfate", section on Adrenal insufficiency and see "Treatment of adrenal insufficiency in adults", section on Androgen replacement).

- In women with secondary adrenal insufficiency, DHEA appears to have a modest beneficial effect on psychological well-being. However, the available data are from women with panhypopituitarism, who have combined adrenal and ovarian androgen deficiency. No data are available in women with isolated ACTH deficiency, a very rare disorder.

To date, studies of DHEA replacement have been small, relatively short-term and mostly in women. There is insufficient evidence to recommend therapy in all patients with adrenal insufficiency, particularly in men.

In women with adrenal insufficiency (primary or secondary), we suggest DHEA therapy only for those who have significantly impaired mood or sense of well-being despite optimal glucocorticoid and mineralocorticoid replacement. We typically start with 25 to 50 mg daily for three to six months and adjust the dose based upon the clinical response (improvement in libido, sense of well-being, and androgenic side effects). Adverse effects and biochemical monitoring are discussed separately. (See "Dehydroepiandrosterone and its sulfate").

If no obvious benefit has been seen after six months, or if adverse effects occur, we discontinue DHEA. In the United States, this approach is severely limited by the lack of product quality control, as DHEA is considered to be dietary supplement rather than a hormone preparation. Therefore, DHEA supplements available commercially may not actually contain the advertised dose. This topic is discussed in detail separately. (See "Dehydroepiandrosterone and its sulfate").

**Other considerations**

- In all patients, associated disorders should be sought and treated appropriately. For example, patients with secondary adrenal insufficiency should receive evaluation and adequate replacement for
other pituitary hormone deficiencies. Replacement of thyroid hormone without replacement of glucocorticoids can precipitate acute adrenal insufficiency.

- Patients with hypopituitarism who have partial or total ACTH deficiency and are receiving suboptimal cortisol or cortisone replacement may be at risk of developing symptoms of cortisol deficiency when growth hormone therapy is initiated. This is due to the inhibitory effect of growth hormone on 11-beta-hydroxysteroid dehydrogenase type 1, the enzyme that converts cortisone to cortisol [25].

**Illness or surgery** — Cortisol secretion normally increases with the stress of illness and surgery. This fact has prompted the usual clinical practice of giving higher doses of glucocorticoid to patients with adrenal insufficiency in these situations. Unfortunately, there is little information about how much additional glucocorticoid is needed.

**Illness** — During minor illnesses, such as upper respiratory infections, the patient can increase the dosage of glucocorticoid to two to three times the usual daily dosage for three days without consulting a physician (known as the 3 x 3 rule). The increased dosage will decrease fever and malaise and will not compromise the immune response. If the illness becomes worse during the three days or if the patient cannot resume the usual maintenance dosage on the fourth day, he or she should consult a physician to determine if other treatment (eg, antibiotics) is indicated.

As described below, patients with nausea and vomiting who are unable to retain oral medications should have a low threshold for injecting glucocorticoid. Further medical attention should then be sought. (See "Emergency precautions" below).

**Surgery** — The appropriate dose and timing of glucocorticoids for patients undergoing surgery is controversial. Early reports of death after surgery led to a recommendation to give glucocorticoids in doses equivalent to 1000 mg of hydrocortisone daily [32]. This is clearly in excess of the increased production of up to 200 mg daily. Prolonged postoperative pharmacologic glucocorticoid therapy can mask symptoms and signs of infection and cause undesirable side effects. For example, traditional doses of 300-400 solucortef for a few days can cause significant hypokalemia and edema.

Current recommendations for glucocorticoid supplementation at surgery take into account the severity of the operation, and suggest lower daily doses [32,33]. For minor procedures such as herniorrhaphy, a dose equivalent to hydrocortisone 25 mg is suggested for the day of operation only, with a return to the usual replacement dose on the second day. For moderate surgical stress (eg, cholecystectomy, joint replacement), divided intravenous doses
equivalent to hydrocortisone 50 to 75 mg are suggested on the day of surgery and the first post-operative day, with a return to the usual dose on the second post-operative day (using oral or intravenous preparation as appropriate). The authors suggest a total daily dose equivalent to 100 to 150 mg hydrocortisone for major surgical procedures (eg, cardiac bypass) given in divided doses for two to three days, then returning to the usual dose. Alternatively, the dose used on the day of surgery can be halved on post-operative day one.

Limited data from studies in adrenalectomized primates and humans with secondary adrenal insufficiency suggest that supraphysiologic glucocorticoid doses may not be required to survive surgery successfully [3,5]. As an example, one study randomly assigned patients with adrenal insufficiency caused by chronic glucocorticoid therapy to receive either intravenous hydrocortisone or saline during elective surgery (in addition to their usual daily prednisone dose of 7.5 mg or more) [3]. There was no difference in the occurrence of hypotension (one in each group) or in the perioperative pulse rates or blood pressures. These data need to be confirmed before supplementation is not routinely provided.

Emergency precautions — The major risk to the patient with adrenal insufficiency is the lack of a normal serum cortisol response to stress and, in patients with primary adrenal insufficiency, of a normal renin-angiotensin-aldosterone response to hypovolemia. Consequently, the patient must anticipate these situations and be prepared to modify therapy to meet these needs.

- Every patient should wear a medical alert (Medic Alert) bracelet or necklace and carry the Emergency Medical Information Card that is supplied with it. Both should indicate the diagnosis, the daily medications and doses, and the physician to call in the event of an emergency.

- Each patient should have injectable glucocorticoid, such as 100 mg vials of solu-cortef or 4 mg vials of dexamethasone, along with vials of sterile 0.9 percent normal saline and syringes. The patient and one or more responsible family or household members should be instructed on how to reconstitute and inject the medication subcutaneously or intramuscularly anywhere on the patient's body if any of the following occur:
  - An injury with substantial blood loss (more than a cup) or fracture
  - Nausea and vomiting and inability to retain oral medications
  - Symptoms of acute adrenal insufficiency
• The patient is found unresponsive

Patient and family instruction should include the need to get medical help immediately after the injection. The patient should be instructed to have a low threshold for injecting the glucocorticoid: if it might be necessary, it should be injected and medical attention should be sought. It is unlikely, however, that a patient will need the injectable glucocorticoid more than two or three times a year, and most patients go for years without using it.

Critical illness — Adrenal cortisol secretion increases during critical illness, but the increase may not be detected if only total serum cortisol concentrations are measured. Some critically ill patients may have "functional adrenal insufficiency", but there is currently no consensus on diagnostic criteria or indications for treatment. This topic is discussed in detail separately. (See "Glucocorticoid therapy in septic shock", section on Functional adrenal insufficiency and see "Evaluation of the response to ACTH in adrenal insufficiency").

PREGNANCY — Pregnancy complicated by primary adrenal insufficiency has been reported in about 100 women [34]. 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 fetal growth retardation was common [35-37]. At present, most women adequately treated for adrenal insufficiency go through pregnancy, labor, and delivery without difficulty, and babies achieve a normal birth weight. The usual glucocorticoid and mineralocorticoid replacement doses are continued; an occasional woman requires slightly more glucocorticoid in the third trimester [30,34,38].

• During labor, adequate saline hydration and 25 mg hydrocortisone should be administered intravenously every six hours.

• At the time of delivery, or if labor is prolonged, hydrocortisone should be administered intravenously in a dose of 100 mg every six hours or as a continuous infusion.

• After delivery, the dosage can be tapered rapidly to maintenance within three days [39].

An occasional woman with severe nausea and vomiting in the first trimester may require intramuscular dexamethasone at a slightly increased dosage (1 mg daily).

The regulation of plasma volume during pregnancy is complex. Secondary hyperaldosteronism is normal [40], associated with increased plasma renin activity and serum aldosterone concentrations [41,42]. Serum concentrations of progesterone, which competes with aldosterone for binding to the type 1
corticosteroid (mineralocorticoid) receptor in the kidney and has a natriuretic effect, are increased throughout pregnancy [43,44]. Plasma atrial natriuretic peptide concentrations reach their nadir late in the third trimester [45], when plasma renin activity and serum aldosterone concentrations reach their peak [41].

There are no studies of mineralocorticoid requirement during pregnancy in women with adrenal insufficiency. Patients should be followed closely throughout pregnancy for electrolyte abnormalities and signs of volume depletion. Plasma renin activity may be used as an index of adequate fludrocortisone dosage, but should not be suppressed to values less than those in pregnant women without adrenal insufficiency (ie, 20 to 25 ng/mL per hour supine or standing) [41,42,45].

**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 [46]. Subsequent reports after glucocorticoids became available for treatment suggested that patients with autoimmune adrenal insufficiency should have a normal life-span and can lead a fully active life, including vigorous exercise [38,46]. By contrast, a recent study based on the Swedish death registry found that patients with adrenal insufficiency have a two-fold higher mortality rate than the background population [47]. The reasons for this discrepancy are not understood and further studies are needed to evaluate whether these patients have premature mortality.

Recent studies report significantly reduced subjective quality of life, and increased rates of work disability in patients with adrenal insufficiency. A Norwegian study of 79 patients who answered a postal survey showed impaired general health and vitality perception, and an increase in reported fatigue. Self-perception of physical functioning was low in women. Working disability at ages 18 to 67 years was 26 percent, compared with 10 percent in the corresponding general Norwegian population [48]. 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 [49]. It is possible that improved therapy that better mimics the normal diurnal cortisol rhythm, or additional therapy with DHEA might ameliorate this problem, but data are not available to address this.

One study noted the presence of heart failure in 7 of 22 patients with long-standing primary adrenal insufficiency receiving conventional treatment after a mean of 26 years [30]. However, the causal relationship, if any, to the adrenal insufficiency or its therapy is unclear.

Linear growth and pubertal development proceed normally in correctly (ie, adequately but not overly) treated children with adrenal insufficiency [50,51].
As noted, over-replacement can lead to bone loss and osteoporosis [19,20].

**SUMMARY AND RECOMMENDATIONS**

**Acute** — Adrenal crisis is a life-threatening emergency that requires immediate treatment (see table 1). (See "Adrenal crisis" above).

- The goal of therapy is treatment of hypotension and reversal of electrolyte abnormalities and of cortisol deficiency. Large volumes (1 to 3 liters) of 0.9 percent saline solution or 5 percent dextrose in 0.9 percent saline should be infused intravenously to correct hypovolemia and hyponatremia associated with mineralocorticoid deficiency and/or SIADH.

- It is essential that treatment of patients who present in possible adrenal crisis not be delayed while diagnostic tests are performed.

- In a patient without a previous diagnosis of adrenal insufficiency, dexamethasone, which is not measured in cortisol assays, should be used rather than hydrocortisone if biochemical testing is performed. (See "Adrenal crisis" above).

- For patients with a previously known diagnosis of adrenal insufficiency, any intravenous glucocorticoid preparation may be used, because diagnostic testing is not necessary.

- Mineralocorticoid administration is not necessary in the acute setting. (See "Adrenal crisis" above).

**Chronic**

- We suggest replacement with hydrocortisone in three divided doses as the glucocorticoid of choice for the management of chronic primary adrenal insufficiency (Grade 2C). A daily dose of dexamethasone or prednisone may also be used. We suggest using the lowest glucocorticoid dose that relieves symptoms of glucocorticoid deficiency.

- Measurement of early morning plasma ACTH concentration is not helpful in patients with secondary adrenal insufficiency, because values are expected to be low. In patients with primary adrenal insufficiency, measurement of early morning plasma ACTH concentration is not necessary for routine monitoring, but may detect over-replacement, in which case the value will be in the low normal range.

- Measurement of urine cortisol excretion does not assist in dose-titration of hydrocortisone.

- The vast majority of patients with primary adrenal insufficiency
eventually require mineralocorticoid replacement with fludrocortisone.

We suggest adjusting the fludrocortisone dose to lower the plasma renin activity to the upper normal range (Grade 2B). (See "Mineralocorticoid replacement" above).

- We suggest DHEA therapy only in women with impaired mood or sense of well-being despite optimal glucocorticoid and, if needed, mineralocorticoid replacement. However, this approach is limited by the lack of reliable source of this compound in some countries (Grade 2B). (See "Androgen replacement" above).

- For minor illnesses, we suggest two-three times the usual maintenance glucocorticoid dosage for three days (known as the 3 x 3 rule) (Grade 2C). (See "Illness or surgery" above).

- For surgical procedures or severe illness we suggest coverage with graded doses of hydrocortisone or its equivalent, as noted above.

- All patients should wear a medical alert bracelet and have supplies for emergency glucocorticoid injections.

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34. Lindsay, JR, Nieman, LK. The hypothalamic-pituitary-adrenal axis in pregnancy: challenges in disease detection and treatment. Endocr Rev
**GRAPHICS**

**Treatment of acute adrenal insufficiency (adrenal crisis)**

<table>
<thead>
<tr>
<th>Emergency measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Establish intravenous access with a large-gauge needle.</td>
</tr>
<tr>
<td>2. Draw blood for stat serum electrolytes and glucose and routine measurement of plasma cortisol and ACTH. Do not wait for lab results.</td>
</tr>
<tr>
<td>3. Infuse 2 to 3 liters of isotonic saline or 5 percent dextrose in isotonic saline as quickly as possible. Monitor for signs of fluid overload by measuring central or peripheral venous pressure and listening for pulmonary râles. Reduce infusion rate if indicated.</td>
</tr>
<tr>
<td>4. Inject 4 mg of dexamethasone phosphate intravenously. Intravenous hydrocortisone (100 mg immediately and every 6 h thereafter) may also be used, but will interfere with measurement of plasma cortisol during the short ACTH stimulation test. Mineralocorticoids are unnecessary at this time.</td>
</tr>
<tr>
<td>5. Use supportive measures as needed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subacute measures after stabilization of the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Continue intravenous isotonic saline at a slower rate for next 24 to 48 h.</td>
</tr>
<tr>
<td>2. Search for and treat possible infectious precipitating causes of the adrenal crisis.</td>
</tr>
<tr>
<td>3. Perform a short ACTH stimulation test to confirm the diagnosis of adrenal insufficiency, if patient does not have known adrenal insufficiency.</td>
</tr>
<tr>
<td>4. Determine the type of adrenal insufficiency and its cause if not already known.</td>
</tr>
<tr>
<td>5. Taper glucocorticoids to maintenance dosage over 1 to 3 d, if precipitating or complicating illness permits.</td>
</tr>
<tr>
<td>6. Begin mineralocorticoid replacement with fludrocortisone (0.1 mg by mouth daily) when saline infusion is stopped.</td>
</tr>
</tbody>
</table>
### Comparison of commonly used glucocorticoid preparations

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Approximate equivalent dose, mg</th>
<th>Relative potency</th>
<th>Mineralocorticoid activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>20</td>
<td>1.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25</td>
<td>0.8</td>
<td>Yes</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>4.0</td>
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<tr>
<td>Prednisolone</td>
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</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
<td>5.0</td>
<td>No</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>30-150</td>
<td>No</td>
</tr>
</tbody>
</table>

### Treatment of chronic primary adrenal insufficiency

#### Glucocorticoid replacement

1. Dexamethasone 0.5 (0.25-0.75) mg or prednisone 5 (2.5-7.5) mg orally at bedtime. Supplement with hydrocortisone 5-10 mg orally in mid-afternoon if indicated.

2. Alternative therapy is with hydrocortisone 15-20 mg upon awakening and 5-10 mg in early afternoon.

3. Monitor clinical symptoms and morning plasma ACTH.

#### Mineralocorticoid replacement

1. Fludrocortisone 0.1 (0.05-0.2) mg orally.

2. Liberal salt intake.

3. Monitor lying and standing blood pressure and pulse, edema, serum potassium and plasma renin activity.

#### Androgen replacement

1. Dehydroepiandrosterone 25-50 mg orally in women.
**Patient education**

1. Educate patient about the disease, how to manage minor illnesses and major stresses and how to inject dexamethasone intramuscularly.

**Emergency precautions**

1. Obtain Medic-Alert bracelet/necklace, Emergency Medical Information Card, and prefilled syringes containing dexamethasone 4 mg in 1 mL saline.

**Treatment of minor febrile illness or stress**

1. Increase glucocorticoid dose 2 to 3 fold for the few days of illness. Do not change mineralocorticoid dose.
2. Contact physician if illness worsens or persists for more than 3 d.
3. No extra supplementation is needed for most uncomplicated, outpatient dental procedures under local anesthesia. General anesthesia or intravenous sedation should not be used in the office.

**Emergency treatment of severe stress or trauma**

1. Inject contents of prefilled dexamethasone (4 mg) syringe intramuscularly.
2. Get to physician as quickly as possible.

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**Grade 2C recommendation**

A Grade 2C recommendation is a very weak recommendation; other alternatives may be equally reasonable.

**Explanation:**
A Grade 2 recommendation is a weak recommendation. It means "this is our suggestion, but you may want to think about it." It is unlikely that you should follow the suggested approach in all your patients, and you might reasonably choose an alternative approach. For Grade 2 recommendations, benefits and risks may be finely balanced, or the benefits and risks may be uncertain. In deciding whether to follow a Grade 2 recommendation in an individual patient, you may want to think about your patient's values and preferences or about your patient's risk aversion.

Grade C means the evidence comes from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.

**Recommendation grades**

1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients
2. Weak recommendation: Benefits and risks closely balanced and/or uncertain

**Evidence grades**

A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form
B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form
C. Low-quality evidence: Evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws

For a complete description of our grading system, please see the UpToDate editorial policy which can be found by clicking "About UpToDate" and then selecting "Policies".

**Grade 2B recommendation**

A Grade 2B recommendation is a weak recommendation; alternative approaches may be better for some patients under some circumstances.

**Explanation:**
A Grade 2 recommendation is a weak recommendation. It means "this is our suggestion, but you may want to think about it." It is unlikely that you should follow the suggested approach in all your patients, and you might reasonably choose an alternative approach. For Grade 2 recommendations, benefits and risks may be finely balanced, or the benefits and risks may be uncertain. In deciding whether to follow a Grade 2 recommendation in an individual patient, you may want to think about your patient's values and preferences or about your patient's risk aversion.

Grade B means that the best estimates of the critical benefits and risks come from randomized, controlled trials with important limitations (eg, inconsistent results, methodologic flaws, imprecise results, extrapolation from a different population or setting) or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimates of benefit and risk, and may change the estimates.

**Recommendation grades**
1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients
2. Weak recommendation: Benefits and risks closely balanced and/or uncertain

**Evidence grades**
A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form
B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form
C. Low-quality evidence: Evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws

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