Chapter 18: Adrenal Gland Disorders

INTRODUCTION

- Hyperfunction of the adrenal glands involves excess production of the adrenal hormones cortisol (resulting in Cushing syndrome) or aldosterone (resulting in hyperaldosteronism).
- Adrenal gland hypofunction is associated with primary (Addison disease) or secondary adrenal insufficiency.

CUSHING SYNDROME: PATHOPHYSIOLOGY

- Cushing syndrome results from effects of supraphysiologic glucocorticoid concentrations originating from either exogenous administration or endogenous overproduction by the adrenal gland (adrenocorticotropic hormone [ACTH] dependent) or by abnormal adrenocortical tissues (ACTH independent).
- ACTH-dependent Cushing syndrome (80% of all Cushing syndrome cases) is usually caused by overproduction of ACTH by the pituitary gland, causing bilateral adrenal hyperplasia. Pituitary adenomas account for about 85% of these cases (Cushing disease). Ectopic ACTH-secreting tumors and nonneoplastic corticotropin hypersecretion cause the remaining 20% of ACTH-dependent cases.
- Ectopic ACTH syndrome refers to excessive ACTH production resulting from an endocrine or nonendocrine tumor, usually of the pancreas, thyroid, or lung (eg, small-cell lung cancer).
- ACTH-independent Cushing syndrome is usually caused by adrenal adenomas and carcinomas.

CLINICAL PRESENTATION

- The most common findings in Cushing syndrome are central obesity and facial rounding (90% of patients). Peripheral obesity and fat accumulation occur in 50% of patients. Fat accumulation in the dorsocervical area (buffalo hump) is nonspecific, but increased supraclavicular fat pads are more specific for Cushing syndrome. Patients are often described as having moon facies and a buffalo hump.
- Other findings may include myopathy or muscular weakness, abdominal striae, hypertension, glucose intolerance, psychiatric changes, gonadal dysfunction, facial plethora (reddish complexion), and amenorrhea and hirsutism in women.
- Up to 60% of patients develop Cushing-induced osteoporosis; about 40% present with back pain; and 20% progress to spinal compression fractures.

DIAGNOSIS

- Hypercortisolism can be established with one or more of the following tests: 24-hour urinary free cortisol (UFC), midnight plasma cortisol, late-night (11 PM) salivary cortisol, and/or low-dose dexamethasone suppression test (DST).
- Other tests to determine etiology are plasma ACTH; adrenal vein catheterization; metyrapone stimulation test; adrenal, chest, or abdominal computed tomography (CT); corticotropin-releasing hormone (CRH) stimulation test; inferior petrosal sinus sampling; and pituitary magnetic resonance imaging (MRI).
- Adrenal nodules and masses are identified using high-resolution CT scanning or MRI.

TREATMENT

- Goals of Treatment: Limit morbidity and mortality and return the patient to a normal functional state by removing the source of hypercortisolism while minimizing pituitary or adrenal deficiencies.
- Treatment plans in Cushing syndrome based on etiology are included in **Table 18-1**.

TABLE 18-1

Treatment Options in Cushing Syndrome Based on Etiology

Etiology	Nondrug	Generic (Brand) Drug Name	Dosing		
			Initial Dose	Usual Range	Maximum
Ectopic ACTH syndrome	Surgery, chemotherapy, irradiation	Metyrapone (Metopirone) 250 mg capsules	0.5–1 g/day, divided every 4–6 hours	1–2 g/day, divided every 4–6 hours	6 g/day
		Ketoconazole (Nizoral) 200 mg tablets	200 mg once or twice a day	200–1200 mg/day, divided twice daily	1600 mg/day divided four times daily
Pituitary dependent	Surgery, irradiation	Mitotane (Lysodren) 500 mg tablets	0.5–1 g/day, increased by 0.5–1 g/day every 1–4 weeks	1–4 g daily, with food to decrease GI effects	12 g/day
		Metyrapone	See above	See above	See above
		Mifepristone (Korlym) 300 mg tablets	300 mg once daily, increased by 300 mg/day every 2–4 weeks	600–1200 mg/day	1200 mg/day or 20 mg/kg/day
		Cabergoline (Dostinex) 0.5 mg tablets	0.5 mg once weekly	0.5–7 mg once weekly	7 mg/week
		Pasireotide (Signifor) 0.3, 0.6, and 0.9 mg/mL solution	0.6–0.9 mg twice daily	0.3–0.9 mg twice daily	1.8 mg/day
Adrenal adenoma	Surgery, postoperative replacement	Ketoconazole	See above	See above	See above
Adrenal carcinoma	Surgery	Mitotane	See above	See above	See above

ACTH, adrenocorticotropic hormone.

Nonpharmacologic Therapy

- Treatment of choice for both ACTH-dependent and ACTH-independent Cushing syndrome is surgical resection of offending tumors.
- Transsphenoidal resection of the pituitary tumor is the treatment of choice for Cushing disease. Radiotherapy may be preferred for tumors invading the dura or cavernous sinus and provides clinical improvement in ~50% of patients within 3–5 years but increases the risk for pituitary-

dependent hormone deficiencies (hypopituitarism).

- Laparoscopic adrenalectomy is often preferred for unilateral adrenal adenomas or when transsphenoidal surgery and pituitary radiotherapy have failed or cannot be used.

Pharmacologic Therapy

- Pharmacotherapy is generally used as second-line treatments in patients who are not surgical candidates and may also be used preoperatively or as adjunctive therapy in postoperative patients awaiting response (**Table 18-1**). Rarely, monotherapy is used as a palliative treatment when surgery is not indicated.

Steroidogenesis Inhibitors

- **Metyrapone** inhibits 11 β-hydroxylase, thereby inhibiting cortisol synthesis. After administration, a sudden decrease in cortisol concentration prompts a compensatory rise in plasma ACTH levels. With cortisol synthesis blocked, adrenal steroidogenesis shunts toward androgen production, resulting in androgenic side effects such as acne and hirsutism. Inhibition of aldosterone synthesis can result in natriuresis and blood pressure changes. Nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, and allergic rash have been reported after oral administration. Metyrapone is currently available through the manufacturer only for compassionate use.

- **Ketoconazole** inhibits cytochrome P-450 enzymes, including 11 β-hydroxylase and 17 α-hydroxylase. It is effective in lowering serum cortisol levels after several weeks of therapy. It also has antiandrogenic activity, which may be beneficial in women but can cause gynecomastia and hypogonadism in men. The most common adverse effects are reversible elevation of hepatic transaminases, GI discomfort, and dermatologic reactions. Because of the risk of severe hepatotoxicity, monitoring should include liver function tests at baseline followed by weekly monitoring of serum ALT throughout therapy. Ketoconazole may be used concomitantly with metyrapone to achieve synergistic reduction in cortisol levels; in addition, ketoconazole's antiandrogenic actions may offset the androgenic potential of metyrapone.

- **Etomidate** is an imidazole derivative similar to ketoconazole that inhibits 11 β-hydroxylase and may have other mechanisms. Because it is only available in a parenteral formulation, use is limited to patients with acute hypercortisolemia requiring emergency treatment or in preparation for surgery. Frequent monitoring of serum cortisol is advised to prevent hypocortisolemia. Side effects include sedation, injection site pain, hypotension, myoclonus, nausea, and vomiting. The initial dose is 0.03 mg/kg by IV bolus followed by a continuous infusion of 0.1–0.3 mg/kg/hr.

Adrenolytic Agents

- **Mitotane** is a cytotoxic drug that inhibits the 11-hydroxylation of 11-deoxycortisol and 11-desoxycorticosterone in the adrenal cortex, reducing synthesis of cortisol and corticosterone. Similar to ketoconazole, mitotane takes weeks to months to exert beneficial effects. Sustained cortisol suppression occurs in most patients and may persist after drug discontinuation in up to one-third of patients. Mitotane degenerates cells within the zona fasciculata and reticularis, resulting in atrophy of the adrenal cortex; the zona glomerulosa is minimally affected during acute therapy but can be damaged during long-term treatment. Mitotane can cause significant neurologic and GI side effects, and patients should be monitored carefully or hospitalized when initiating therapy. Nausea and diarrhea are common at doses greater than 2 g/day and can be avoided by gradually increasing the dose and/or administering it with food. Lethargy, somnolence, and other CNS effects are also common. Reversible hypercholesterolemia and prolonged bleeding times can occur.

Neuromodulators of ACTH Release

- Pituitary secretion of ACTH is normally mediated by neurotransmitters such as serotonin, γ-aminobutyric acid (GABA), acetylcholine, and catecholamines. Although ACTH-secreting pituitary tumors (Cushing disease) self-regulate ACTH production to some degree, these neurotransmitters can still promote pituitary ACTH production. Consequently, agents that target these transmitters have been proposed for treatment of Cushing disease, including cyproheptadine, bromocriptine, cabergoline, valproic acid, octreotide, lanreotide, pasireotide, rosiglitazone, and tretinoin. With the exception of pasireotide, none of these drugs have demonstrated consistent clinical efficacy for treating Cushing disease.

- **Cyproheptadine**, a nonselective serotonin receptor antagonist and anticholinergic drug, can decrease ACTH secretion in some patients with

Cushing disease. However, side effects such as sedation and weight gain significantly limit its use.

- **Pasireotide** (Signifor) is a somatostatin analogue that binds and activates somatostatin receptors, thereby inhibiting ACTH secretion, leading to decreased cortisol secretion. It is approved for treatment of adults with Cushing disease for whom pituitary surgery is not an option or has not been curative. Side effects include nausea, diarrhea, cholelithiasis, increased hepatic transaminases, hyperglycemia, sinus bradycardia, and QT prolongation.

Glucocorticoid-Receptor Blocking Agents

- **Mifepristone** (Korlym) is a progesterone- and glucocorticoid-receptor antagonist that inhibits dexamethasone suppression and increases endogenous cortisol and ACTH levels in normal subjects. Evidence suggests that mifepristone is highly effective in reversing the manifestations of hypercortisolism (hyperglycemia, hypertension, and weight gain). It is FDA approved for treatment of endogenous Cushing syndrome in patients who have type 2 diabetes or glucose intolerance and who are not eligible for, or have had poor response to, surgery. Common adverse effects include fatigue, nausea, headache, arthralgia, peripheral edema, endometrial hyperplasia, and hypokalemia.

EVALUATION OF THERAPEUTIC OUTCOMES

- Close monitoring of 24-hour UFC and serum cortisol is essential to identify adrenal insufficiency in patients with Cushing syndrome. Monitor steroid secretion with all drug therapy (except mifepristone) and give corticosteroid replacement if needed.

HYPERALDOSTERONISM: PATHOPHYSIOLOGY

- Hyperaldosteronism involves excess aldosterone secretion and is categorized as either primary (stimulus arising from within the adrenal gland) or secondary (stimulus from extra-adrenal etiologies).

- *Primary hyperaldosteronism* (PA) is usually caused by bilateral adrenal hyperplasia and aldosterone-producing adenoma (Conn syndrome). Rare causes include unilateral (primary) adrenal hyperplasia, adrenal cortex carcinoma, renin-responsive adrenocortical adenoma, and three forms of familial hyperaldosteronism (FH): Type I (glucocorticoid-remediable aldosteronism); Type II (familial occurrence of adenoma or hyperplasia type II); and Type III.

- *Secondary hyperaldosteronism* results from excessive stimulation of the zona glomerulosa by an extra-adrenal factor, usually the renin–angiotensin system. Elevated aldosterone secretion can result from excessive potassium intake, oral contraceptives, pregnancy, and menses. Heart failure, cirrhosis, renal artery stenosis, and Bartter syndrome also can lead to elevated aldosterone concentrations.

CLINICAL PRESENTATION

- Patients may complain of muscle weakness, fatigue, paresthesias, headache, polydipsia, and nocturnal polyuria.

- Signs may include hypertension and tetany/paralysis.

- A plasma aldosterone concentration-to-plasma renin activity (PAC-to-PRA) ratio or aldosterone-to-renin ratio (ARR) >30 ng/dL per ng/(mL·hr) (830 pmol/L per mcg/(L·hr) and a PAC >15 ng/dL (420 pmol/L) is suggestive of PA.

- Other laboratory findings include suppressed renin activity, elevated plasma aldosterone, hypernatremia (>142 mEq/L), hypokalemia, hypomagnesemia, elevated serum bicarbonate (>31 mEq/L), and glucose intolerance.

DIAGNOSIS

- Initial diagnosis is made by screening patients with suspected PA. Any patient with a blood pressure >150/100 mm Hg measured on 3 separate days and those with resistant hypertension should be screened. Additional patients at risk for PA include those with diuretic-induced hypokalemia, hypertension and adrenal incidentaloma, hypertension and sleep apnea, hypertension and a family history of early onset hypertension or cerebrovascular accident at an age <40 years, and all patients with hypertension and a first-degree relative diagnosed with PA.

- Screening for PA is most often done using the PAC-to-PRA ratio (also known as the ARR). An elevated ARR is highly suggestive of PA.
- If the ARR is positive, confirmatory tests to exclude false-positives include the oral sodium-loading test, saline infusion test, fludrocortisone suppression test (FST), and captopril challenge test. A positive test indicates autonomous aldosterone secretion under inhibitory pressures and is diagnostic for PA.

TREATMENT

Nonpharmacologic Therapy

- Aldosterone-producing adenomas are treated by laparoscopic resection of the tumor, leading to permanent cures in up to 72% of patients. Medical management with an aldosterone receptor antagonist is often effective if surgery is contraindicated.

Pharmacologic Therapy

- Aldosterone-receptor antagonists are the treatment of choice for bilateral adrenal hyperplasia.

  ✔ **Spironolactone** (Aldactone) is a nonselective aldosterone receptor antagonist that competes with aldosterone for binding at aldosterone receptors, thus preventing the negative effects of aldosterone receptor activation. The initial dose is 25 mg once daily titrated upward at 4- to 8-week intervals. Most patients respond to doses between 25 and 400 mg/day given in single or divided doses. Adverse effects include GI discomfort, impotence, gynecomastia, menstrual irregularities, and hyperkalemia.

  ✔ **Eplerenone** (Inspra) is a selective aldosterone receptor antagonist with high affinity for aldosterone receptors and low affinity for androgen and progesterone receptors. Consequently, it elicits fewer sex-steroid–dependent effects than spironolactone. Dosing starts at 50 mg daily, with titration at 4- to 8-week intervals to 50 mg twice a day; some patients may require total daily doses as high as 200–300 mg.

  ✔ **Amiloride** (Amiloride), a potassium-sparing diuretic, is less effective than spironolactone, and patients often require additional therapy to adequately control blood pressure. The initial dose is 5 mg twice daily, with a usual range of 20 mg/day given in two divided doses; doses up to 30 mg/day may be necessary.

  ✔ Additional second-line options include calcium channel blockers, ACE inhibitors, and diuretics such as chlorthalidone, although all of these lack outcome data in PA.

- Treatment of secondary aldosteronism is dictated by etiology. Control or correction of the extra-adrenal stimulation of aldosterone secretion should resolve the disorder. Medical therapy with spironolactone is undertaken until the etiology is identified.

ADRENAL INSUFFICIENCY: PATHOPHYSIOLOGY

- Primary adrenal insufficiency (Addison disease) usually involves destruction of all regions of the adrenal cortex. There are deficiencies of cortisol, aldosterone, and the various androgens, and levels of CRH and ACTH increase in a compensatory manner.
- Autoimmune dysfunction is responsible for 80%–90% of cases in developed countries, whereas tuberculosis is the predominant cause in developing countries.
- Medications that inhibit cortisol synthesis (eg, ketoconazole) or accelerate cortisol metabolism (eg, phenytoin, rifampin, phenobarbital) can also cause primary adrenal insufficiency.
- Secondary adrenal insufficiency most commonly results from exogenous corticosteroid use, leading to suppression of the hypothalamic–pituitary–adrenal axis and decreased ACTH release as well as impaired androgen and cortisol production. Mirtazapine and progestins (eg, medroxyprogesterone acetate, megestrol acetate) have also been reported to induce secondary adrenal insufficiency. Secondary disease typically presents with normal mineralocorticoid concentrations.

CLINICAL PRESENTATION

- Patients with adrenal insufficiency commonly complain of weakness, weight loss, GI symptoms, salt craving, headaches, memory impairment, depression, and postural dizziness.
- Early symptoms of acute adrenal insufficiency also include myalgias, malaise, and anorexia. As the situation progresses, vomiting, fever, hypotension, and shock develop.
- Signs of adrenal insufficiency include increased skin pigmentation, postural hypotension, fever, decreased body hair, vitiligo, amenorrhea, and cold intolerance.

DIAGNOSIS

- The short cosyntropin stimulation test can be used to assess patients with suspected hypercortisolism. An increase to a cortisol level of ≥18 mcg/dL (500 nmol/L) rules out adrenal insufficiency.
- Patients with Addison disease have an abnormal response to the short cosyntropin stimulation test. Plasma ACTH levels are usually elevated (400–2000 pg/mL or 88–440 pmol/L) in primary insufficiency versus normal to low (5–50 pg/mL or 1.1–11 pmol/L]) in secondary insufficiency. A normal cosyntropin-stimulation test does not rule out secondary adrenal insufficiency.
- Other tests include the insulin hypoglycemia test, the metyrapone test, and the CRH stimulation test.

TREATMENT

- Goals of Treatment: Limit morbidity and mortality, return the patient to a normal functional state, and prevent episodes of acute adrenal insufficiency.

Nonpharmacologic Therapy

- Inform patients of treatment complications, expected outcomes, proper medication administration and adherence, and possible side effects.

Pharmacologic Therapy

Corticosteroids

- The agents of choice are **hydrocortisone** and **cortisone acetate**, usually administered two times daily, with the goal of establishing the lowest effective dose while mimicking the normal diurnal adrenal rhythm. Once-daily **prednisolone** is an alternative when adherence to a multidose regimen is a concern.
- Recommended starting total daily doses are hydrocortisone 15–25 mg daily, which is approximately equivalent to cortisone acetate 20–35 mg daily, or prednisolone 3–5 mg daily (**Table 18-2**). For hydrocortisone or cortisone, two-thirds of the dose is given in the morning and one-third is given 6–8 hours later.
- Monitor the patient's symptoms every 6–8 weeks to assess proper glucocorticoid replacement. Measure body weight, postural blood pressures, subjective energy levels, and signs of glucocorticoid excess.
- In primary adrenal insufficiency, **fludrocortisone acetate** 0.05–0.2 mg orally once daily can be used to replace mineralocorticoid loss and maintain volume status. If parenteral therapy is needed, 2–5 mg of **deoxycorticosterone trimethylacetate** in oil can be administered intramuscularly every 3–4 weeks. Mineralocorticoid replacement attenuates development of hyperkalemia, and patients on fludrocortisone therapy do not need to restrict salt intake. Mineralocorticoid therapy may be unnecessary in some cases because glucocorticoids (especially in large doses) also bind to mineralocorticoid receptors.
- Because most adrenal crises occur because of glucocorticoid dose reductions or lack of stress-related dose adjustments, patients receiving

corticosteroid replacement therapy should add 5–10 mg hydrocortisone (or equivalent) to their normal daily regimen shortly before strenuous activities, such as exercise. During times of severe physical stress (eg, febrile illness, injury), patients should be instructed to double their daily dose until recovery.

- Treatment of secondary adrenal insufficiency is similar to primary disease treatment, except that mineralocorticoid replacement is usually not necessary.

TABLE 18-2

Relative Potencies of Glucocorticoids

Glucocorticoid	Anti-inflammatory Potency	Equivalent Potency (mg)	Approximate Half-Life (min)	Sodium-Retaining Potency
Cortisone	0.8	25	30	2
Hydrocortisone	1	20	90	2
Prednisone	3.5	5	60	1
Prednisolone	4	5	200	1
Triamcinolone	5	4	300	0
Methylprednisolone	5	4	180	0
Betamethasone	25	0.6	100–300	0
Dexamethasone	30	0.75	100–300	0

Pharmacologic Therapy of Acute Adrenal Insufficiency

- Acute adrenal insufficiency (adrenal crisis or addisonian crisis) represents a true endocrine emergency.
- Stressful situations, surgery, infection, and trauma are potential events that increase adrenal requirements, especially in patients with some underlying adrenal or pituitary insufficiency.
- The most common cause of adrenal crisis is HPA-axis suppression brought on by abrupt withdrawal of chronic glucocorticoid use.
- **Hydrocortisone** given parenterally is the corticosteroid of choice because of its combined glucocorticoid and mineralocorticoid activity. The starting dose is 100 mg IV by rapid infusion, followed by 200 mg over 24 hours as a continuous infusion or intermittent bolus every 6 hours. IV administration is continued for an additional day at a reduced dose of 100 mg over 24 hours. If the patient is stable at that time, oral hydrocortisone can be started at a dose of 50 mg every 6–8 hours, followed by tapering to the individual's chronic replacement needs.
- **Fluid replacement** often is required and can be accomplished with IV dextrose 5% in normal saline solution at a rate to support blood pressure.
- If therapy is needed for hypoglycemia, dextrose 25% in water can be infused at a dose of 2–4 mL/kg (maximum single dose of 25 g dextrose).
- If hyperkalemia is present after the hydrocortisone maintenance phase, additional mineralocorticoid supplementation can be achieved with **fludrocortisone acetate** 0.1 mg daily.
- Patients with adrenal insufficiency should carry a card or wear a bracelet or necklace that contains information about their condition. They should

also have easy access to injectable hydrocortisone or glucocorticoid suppositories in case of an emergency or during times of physical stress, such as febrile illness or injury.

EVALUATION OF THERAPEUTIC OUTCOMES

- The end point of therapy for adrenal insufficiency is difficult to assess in most patients, but a reduction in excess pigmentation is a good clinical marker. Development of features of Cushing syndrome indicates excessive replacement.

See Chapter 93, Adrenal Gland Disorders, authored by Steven M. Smith, Scott G. Garland, and John G. Gums, for a more detailed discussion of this topic.