Chapter 97: Adrenal Gland Disorders

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 18, Adrenal Gland Disorders.

KEY CONCEPTS

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1. Glucocorticoid secretion from the adrenal cortex is stimulated by adrenocorticotropic hormone (ACTH) or corticotropin that is released from the anterior pituitary in response to the hypothalamic-mediated release of corticotropin-releasing hormone (CRH).
2. To ensure the proper treatment of Cushing syndrome requires diagnostic procedures to (1) establish the presence of hypercortisolism and (2) discover the underlying etiology of the disease.
3. The rationale for treating Cushing syndrome is to reduce the morbidity and mortality resulting from disorders such as diabetes mellitus, cardiovascular disease, and electrolyte abnormalities.
4. The treatment of choice for both ACTH-dependent and ACTH-independent Cushing syndrome is surgery. Pharmacologic agents are reserved for adjunctive therapy, refractory cases, or inoperable disease.
5. Pharmacologic agents that may be used to manage the patient with Cushing syndrome include steroidogenesis inhibitors, adrenolytic agents, neuromodulators of ACTH release, and glucocorticoid-receptor blocking agents.
6. Spironolactone, a competitive aldosterone-receptor antagonist, is the drug of choice in bilateral adrenal hyperplasia (BAH)–dependent hyperaldosteronism.
7. Addison disease (primary adrenal insufficiency) is a state of deficiency in cortisol, aldosterone, and various androgens due to the loss of function in all regions of the adrenal cortex.
8. Secondary adrenal insufficiency usually results from exogenous steroid use, leading to hypothalamic–pituitary–adrenal (HPA)–axis suppression followed by a decrease in ACTH release, and low levels of androgens and cortisol.
9. Virilism results from the excessive secretion of androgens from the adrenal gland and often manifests as hirsutism in females.

BEYOND THE BOOK

BEYOND THE BOOK

- Watch the video Primary adrenal insufficiency (Addison disease): pathology, symptoms, diagnosis, treatment by Osmosis.org URL: https://youtu.be/V6XcBp8EV7Q
- Watch the video Cushing syndrome—causes, symptoms, diagnosis, treatment, pathology by Osmosis.org URL: https://youtu.be/ea1sXgd5ui8
- Create a table with mechanisms for drug-induced secondary adrenal insufficiency

INTRODUCTION

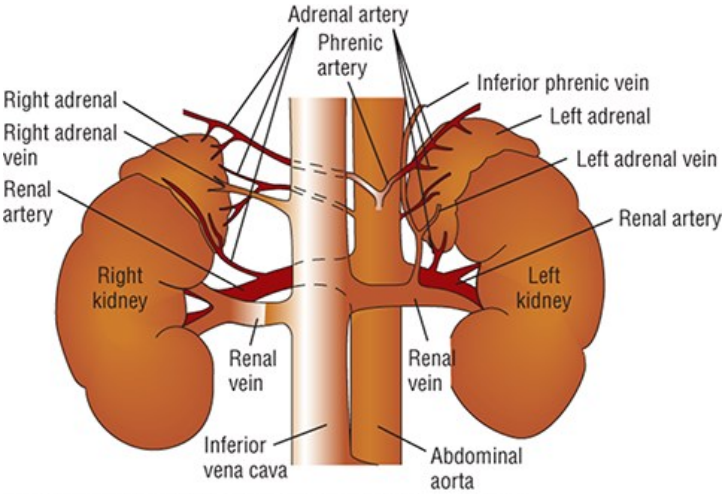
The adrenals are small endocrine glands located atop each kidney that produce several hormones that regulate blood pressure, metabolism, immune response, stress response, and other bodily functions. Under- or over-production of these hormones causes a constellation of symptoms and most commonly results in Cushing syndrome (hypercortisolism), Addison's disease (adrenal insufficiency), or hyperaldosteronism. Adrenal disorders affecting the hormone cortisol are rare, typically effecting fewer than 1 person in a thousand. On the other hand, aldosterone-related disorders, particularly hyperaldosteronism, are relatively common. Left untreated, complications from these disorders can include organ damage, physical manifestations, electrolyte abnormalities, cardiovascular crises, and even death. Thus, prompt identification and treatment is critical. Screening and management of these conditions lower the risk of complication, increase life expectancy, and improve quality of life for those affected.[1]

PHYSIOLOGY, ANATOMY, AND BIOCHEMISTRY

The adrenal glands are located on the upper poles of each kidney (Fig. 97-1). On average, each adrenal gland weighs 4 g and is 2 to 3 cm in width and 4 to 6 cm in length. The gland is fed by small arteries from the abdominal aorta and renal and phrenic arteries. Drainage of the adrenal gland occurs via the renal vein on the left and the inferior vena cava on the right.

FIGURE 97-1

Anatomy of the adrenal gland.

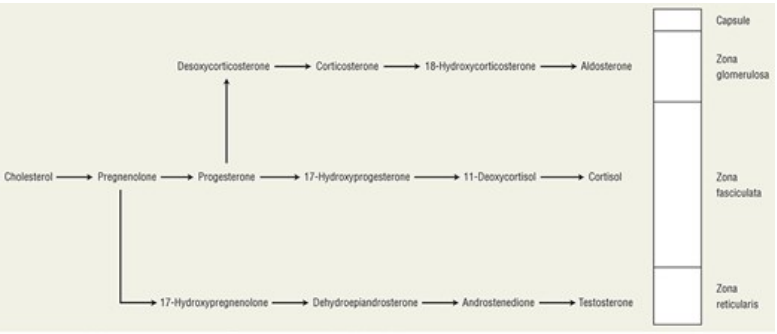


Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The adrenal medulla comprises 10% of the total gland and is responsible for the secretion of catecholamines. The adrenal cortex accounts for the remaining 90% and is responsible for the secretion of three types of hormones (Fig. 97-2) from three separate zones.

FIGURE 97-2

Hormone synthetic pathways in relation to the zones of the adrenal cortex.



The zona glomerulosa accounts for 15% of the total adrenal cortex and is responsible for mineralocorticoid production, of which aldosterone is the principal end product. Aldosterone maintains electrolyte and volume homeostasis by altering potassium and magnesium secretion and renal tubular sodium reabsorption. The zona fasciculata, the middle zone, makes up 60% of the cortex, is high in cholesterol, and is responsible for basal and stimulated glucocorticoid production. Glucocorticoids, mainly cortisol, are responsible for the regulation of fat, carbohydrate, and protein metabolism. The zona reticularis occupies 25% of the adrenal cortex and is responsible for adrenal androgen production. The androgens, testosterone, and estradiol are the major end products and influence the reproductive system in addition to modulating primary and secondary sex characteristics.

Hormone Production and Metabolism

Adrenal steroid hormone synthesis begins with the conversion of cholesterol to pregnenolone by cytochrome P450 (CYP) enzymatic side-chain cleavage (Fig. 97-2). Following this rate-limiting step, pregnenolone is converted to various 19- and 21-carbon steroids, depending on the enzymatic capabilities within each zone of the cortex. Androgenic properties predominate in the 19-carbon steroids, whereas mineralocorticoid and glucocorticoid properties manifest in the 21-carbon steroids.

Aldosterone production is initiated by the 21-hydroxylation of progesterone to form deoxycorticosterone. Subsequently, aldosterone synthase converts deoxycorticosterone to aldosterone through the intermediary, corticosterone. The zona glomerulosa preferentially produces aldosterone for three main reasons. First, the zona glomerulosa lacks 17α-hydroxylase activity and therefore can only convert pregnenolone to progesterone. Second, in contrast to the other zones, cells in the zona glomerulosa possess aldosterone synthase activity, which catalyzes the terminal steps in aldosterone synthesis. Lastly, cells of the zona glomerulosa display a greater number of angiotensin II receptors than cells of the other zones. The binding of angiotensin II to these receptors provides the stimulus for initiating the aldosterone biosynthesis cascade. Thus, aldosterone synthesis is a unique feature of the zona glomerulosa, explaining why aldosterone is not affected during disease processes limited to the zona fasciculata or reticularis.

Cortisol is produced from pregnenolone via four successive hydroxylations. These hydroxylations occur primarily in the zona fasciculata, although the zona reticularis is also capable of producing glucocorticoids.

Androgens, produced primarily in the zona reticularis and less commonly in the zona fasciculata, have a 19-carbon structure and serve as precursors to more potent analogs produced in the periphery. The adrenal gland can synthesize estradiol and estrone from testosterone and androstenedione, respectively; however, the quantities synthesized by the adrenal gland are extremely small. The rates of production for the various steroids produced by the adrenal gland are listed in Table 97-1.

TABLE 97-1

Rates of Adrenal Production and Plasma Concentrations of Various Steroids

Steroid	24-hour Secretion (mg)	Plasma Concentration
Aldosterone	0.15 (0.42 µmol)	2-9 ng/dL (55-250 pmol/L; supine, normal-sodium diet)
Androstenedione	2.2-2.5 (7.7-8.7 µmol)	50-250 ng/dL (1.7-8.7 nmol/L)
Corticosterone	1-4 (3-12 µmol)	2.4 ± 1.5 ng/dL (69 ± 43 nmol/L; female) 4.2 ± 2.2 ng/dL (121 ± 64 nmol/L; male)
Cortisol	8-25 (22-69 µmol)	0-25 µg/dL (0-690 nmol/L)
11-Deoxycorticosterone	0.60 (1.8 µmol)	2-19 ng/dL (60-575 pmol/L)
11-Deoxycortisol	0.40 (1.2 µmol)	12-158 ng/dL (350-4,560 pmol/L)
Progesterone	0	<20 ng/dL (0.6 nmol/L; female)[a] 300-2,000 ng/dL (9.5-64 nmol/L; female)[b] <20-140 ng/dL (0.6-4.5 nmol/L; male)
Testosterone (total)	0.23 (0.8 µmol; female)	6-86 ng/dL (0.2-3.0 nmol/L; female) 270-1,070 ng/dL (9.4-37 nmol/L; male)

[a]Follicular phase of menstrual cycle.

[b]Luteal phase of menstrual cycle.

Data from Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory reference values. N Engl J Med. 2004;351(15):1548-1563.

Glucocorticoid metabolism occurs in the liver and is responsible for converting inactive steroids to active metabolites, as well as modifying active steroids to less active or inactive metabolites. Most pharmaceutical steroid products are active; however, in the case of prednisone and cortisone, metabolism is necessary for conversion to the active prednisolone and cortisol, respectively.

Following metabolic conversion, glomerular filtration is primarily responsible for eliminating endogenously produced glucocorticoids. The half-life of cortisol is 70 to 120 minutes, whereas aldosterone exhibits extremely high intrinsic clearance and a half-life of only 15 minutes.

Metabolism and conversion of the various steroids can be altered by a variety of disease states and medicinal compounds. Drugs known to enhance steroid clearance include phenytoin, phenobarbital, rifampin, and mitotane. Likewise, diseases such as hyperthyroidism and renal disease can enhance steroid clearance. In contrast, drugs such as estrogens and estrogen-containing oral contraceptives reduce steroid clearance. Similarly, liver disease, age, pregnancy, hypothyroidism, anorexia nervosa, protein-calorie malnutrition, and renal disease are associated with reduced steroid clearance.

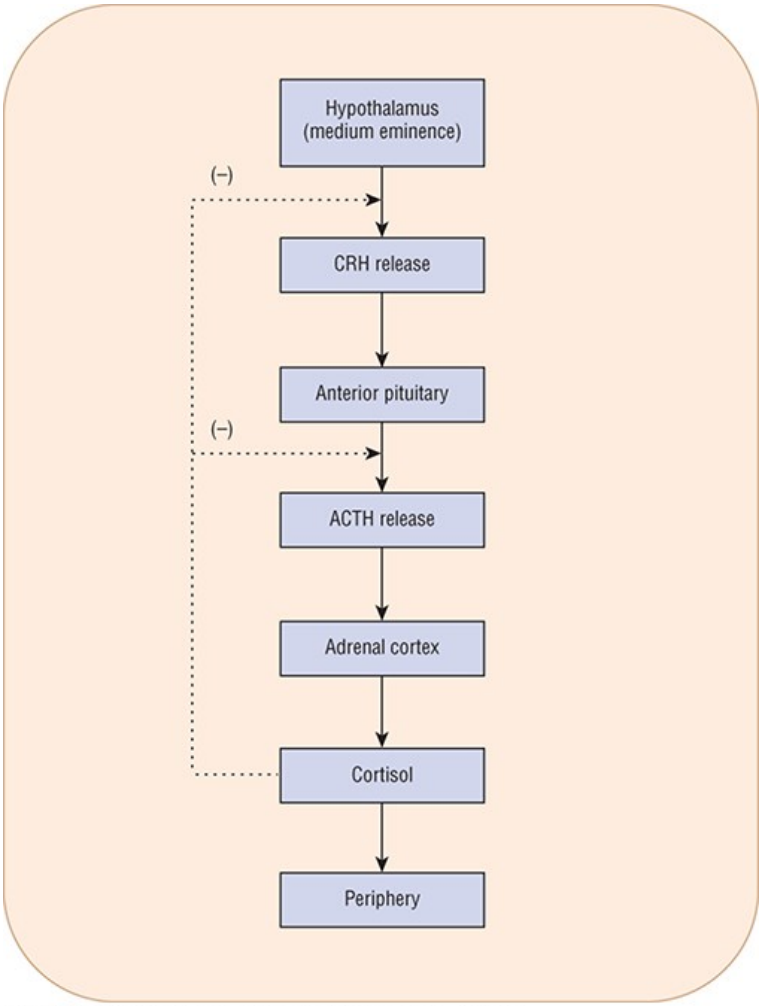
Plasma glucocorticoids are bound to one of three plasma proteins in varying degrees. Corticosteroid-binding globulin (CBG), albumin, and α_1-glycoprotein are capable of binding glucocorticoids, with CBG being the principal binding protein. Steroid binding serves as a reservoir for steroids in their inactive state and more than 95% of cortisol is normally bound. Binding to plasma proteins prevents glucocorticoid activity at receptor-activating sites. Therefore, a final but important variable in the altered plasma concentration of free (active) steroids is the concentration of plasma proteins.

Regulation of Hormone Secretion

1 Glucocorticoid secretion is regulated by the pituitary hormone, adrenocorticotropic hormone (ACTH [also known as corticotropin]). Under normal conditions, ACTH is released from the anterior pituitary in response to corticotropin-releasing hormone (CRH), which is secreted by the median eminence of the hypothalamus (Fig. 97-3). Vasopressin and oxytocin have weak ACTH-releasing activity through binding to the inferior V_3 receptor. CRH, in combination with vasopressin and oxytocin, stimulates greater ACTH secretion than each hormone individually.

FIGURE 97-3

Negative feedback system involved in the regulation of cortisol secretion under normal conditions. (CRH, corticotropin-releaseing hormone; ACTH, adrenocorticotropic hormone)



Additionally, histochemical studies have demonstrated that certain neurotransmitters, such as serotonin and norepinephrine, can stimulate the production of CRH and ACTH. After release, ACTH stimulates the adrenal gland to release cortisol and, to a lesser extent, aldosterone and androgens. The rising cortisol concentration inhibits the secretion of CRH and ACTH through a negative feedback mechanism. In addition, leptin, an adipocyte hormone, has an inhibitory effect on hypothalamic–pituitary–adrenal (HPA) activity.

Adrenal androgens are regulated in a similar fashion to cortisol. When plasma androgen reaches sufficient concentrations, production is terminated via a negative feedback loop. Androgen release is increased during puberty and in women with hirsutism. Adrenal androgen release decreases with

age and in fasting states, including anorexia nervosa.

In contrast to cortisol and adrenal androgens, the regulation of aldosterone secretion is considerably more complex. The renin-angiotensin system regulates aldosterone secretion through both intrarenal and extrarenal mechanisms. Renin production and subsequent aldosterone secretion are stimulated by blood pressure-lowering (due to volume depletion), erect posture, salt depletion, β-adrenergic stimulation, and CNS excitation (see Chapter 30, "Hypertension"). Renin production is inhibited by salt loading, angiotensin II, vasopressin, potassium, calcium, blood pressure increases, and a variety of drugs. The renin-mediated production of angiotensin II is the initial stimulus for aldosterone synthesis. Additionally, angiotensin II can be acted on by aminopeptidase and converted to angiotensin III. Both angiotensin II and III are capable of stimulating the zona glomerulosa to secrete aldosterone. Following aldosterone secretion, increases in renal sodium, water retention, and blood pressure occur thereby turning off the stimulus for renin release.

HYPERFUNCTION OF THE ADRENAL GLAND

Adrenal disorders can be categorized as hyperfunction or hypofunction of the adrenal gland. Hyperfunction of the adrenal gland generally involves excess production of adrenal hormones, most notably cortisol, resulting in Cushing syndrome, or aldosterone, resulting in hyperaldosteronism.

Cushing Syndrome

In 1932, Cushing first described a syndrome of pituitary basophilism that attracted national attention. These patients had unexplained central obesity, cutaneous striae, osteoporosis, weakness, hypertension, diabetes mellitus, and congestion. Cushing believed the disease was of a pituitary origin. Ten years later, Albright focused his attention on the "sugar hormone," which he believed originated from the adrenal cortex.[2] It was not until the development of a method to measure urinary steroids did it become clear that elevated steroids in patients with Cushing syndrome were the result of excess plasma cortisol (hypercortisolism).

Cushing syndrome results from the effects of supraphysiologic concentrations of glucocorticoids originating either from the exogenous administration or, less commonly, endogenous overproduction by the adrenal glands. Excess glucocorticoids are produced in response to the overproduction of ACTH (ACTH-dependent) or by abnormal adrenocortical tissues (ACTH-independent). ACTH-dependent Cushing syndrome (≈80% of all Cushing syndrome cases) usually originates from an overproduction of ACTH by the pituitary gland. Excessive ACTH chronically stimulates the adrenal glands causing bilateral adrenal hyperplasia (BAH). Approximately 85% of these cases are caused by pituitary adenomas (Cushing disease). Ectopic ACTH-secreting tumors and non-neoplastic corticotropin hypersecretion, possibly secondary to excess CRH production, account for the remainder of ACTH-dependent causes.[3] Ectopic ACTH syndrome refers to excessive ACTH production resulting from an endocrine or nonendocrine tumor, usually of the pancreas, thyroid, or lung. Small-cell carcinoma of the lung will lead to ectopic ACTH secretion in 0.5% to 2% of cases, whereas bronchial carcinoid tumors are usually the most common.[4] Distinguishing between the various etiologies requires a careful history and laboratory work (Table 97-2).

TABLE 97-2

Various Etiologies of Cushing Syndrome and Their Respective Differences

	Pituitary-Dependent	Ectopic ACTH Syndrome	Adrenal Adenoma	Adrenal Carcinoma
Course	Slow	Rapid	Slow	Rapid
Symptoms	Mild to moderate	Atypical	Mild to moderate	Severe
Dominant sex/age	Female/male	Male	None noted	Children
Virilization	+	+	+	+++
Abdominal mass	0	0	0	++
Plasma ACTH concentration	Slightly elevated	High	Low	Low
Dexamethasone suppression test	≥50% suppression	No suppression	No suppression	No suppression
Iodocholesterol scan	Bilateral uptake	Bilateral uptake	Unilateral	None

(ACTH, adrenocorticotropic hormone)

The remaining 20% of Cushing syndrome cases are ACTH-independent and divided almost equally between adrenal adenomas and adrenal carcinomas. In rare cases, macronodular hyperplasia, primary pigmented nodular adrenal disease, or McCune–Albright syndrome is the culprit.[3,5] The majority of adrenal cortex tumors are benign adenomas. Adrenal carcinoma is found more often in children than in adults with Cushing syndrome.

Patients with Cushing syndrome commonly present (>90% of patients) with central obesity and facial rounding. Approximately 50% of patients exhibit some peripheral obesity and fat accumulation. Fat accumulation in the dorsocervical area (buffalo hump) is often associated with weight gain, whereas increased supraclavicular fat pads are more specific for Cushing syndrome. Striae are usually present along the lower abdomen and have a red to purple color. Traditionally, complications caused by high blood pressure have been major contributors to the morbidity and mortality of Cushing syndrome. Hypertension is diagnosed in 75% to 85% of patients, with diastolic blood pressures greater than 119 mm Hg noted in over 20% of patients.[6] Glucose intolerance is present in 60% of patients. Thus, many patients meet diagnostic criteria for the metabolic syndrome and have a corresponding increased risk of coronary heart disease (CHD) and stroke. Screening for Cushing syndrome in this population and in patients with uncontrolled diabetes mellitus has been suggested,[7,8] particularly when these conditions surface at an unusually early age.[9] However, screening all patients with type 2 diabetes is likely not cost-effective.[10]

CLINICAL PRESENTATION: Cushing Syndrome

General

- The most common findings, which are present in 90% of patients, are central obesity and facial rounding.

Symptoms

- A majority of patients complain of myopathies and muscular weakness.

Signs

- Peripheral obesity and fat accumulation are found in 50% of patients.
- Facial plethora is caused by underlying atrophy of the skin and connective tissue.
- Patients often are described as having moon faces with a buffalo hump.
- Hypertension is seen in 75% to 85% of patients.
- Psychiatric changes can occur in as many as 55% of patients.
- Approximately 50% to 60% of patients will develop Cushing syndrome–induced osteoporosis. Of these, 40% will present with back pain and 20% will have compression fractures of the spine.
- Gonadal dysfunction is common with amenorrhea seen in up to 75% of females.
- Hirsutism is present in 80% of females.

Laboratory Tests

- A midnight plasma cortisol, late-night salivary cortisol, 24-hour urinary free cortisol (UFC), and/or low-dose dexamethasone suppression test (DST) will establish the presence of hypercortisolism.

Other Diagnostic Tests

- The plasma ACTH test, metyrapone stimulation test, CRH stimulation test, or inferior petrosal sinus sampling (IPSS) will help determine the etiology.

Iatrogenic (exogenous) causes of Cushing syndrome is the most common etiology. Therefore, all patients exhibiting hypercortisolism should undergo a comprehensive history and evaluation assessing medication use before laboratory testing is performed to identify endogenous sources. Iatrogenic Cushing syndrome can occur from the administration of oral, inhaled, intranasal, intra-articular, and topical glucocorticoids, as well as progestins such as medroxyprogesterone acetate and megestrol acetate.[11] Disease severity correlates with exogenous glucocorticoid potency, dose, frequency, route, and treatment duration. Moreover, patients taking CYP3A4 inhibitors concurrently with a glucocorticoid can be at higher risk of developing iatrogenic Cushing syndrome.[12,13] If exogenous glucocorticoids are being taken, the plasma cortisol concentration can increase, while the corticosterone concentration remains low.[14]

In the absence of any known exogenous causes, the clinician will need to differentiate the syndrome from other causes, such as pseudo-Cushing syndrome, that mimic true Cushing syndrome. Patients with obesity, chronic alcoholism, depression, and acute illness of any type can present with certain features of Cushing syndrome. For example, patients who have major depressive disorder may have urinary steroid abnormalities seen in Cushing syndrome, but do not have the cushingoid appearance. In chronic alcoholism, steroid laboratory panels generally return to baseline after ceasing alcohol intake. And obese patients often will have normal cortisol concentrations for both serum and urinary screening tests. Thus, identifying true cases of Cushing syndrome requires a comprehensive history in combination with laboratory and possibly imaging assessment.

2 The diagnosis of Cushing syndrome involves two steps: (a) establishing the presence of hypercortisolism, which is relatively easy, and (b) determining the etiology, which can be challenging (Fig. 97-4).[5,8,15] The presence of hypercortisolism can be established via one or more of the following tests: 24-hour UFC, midnight plasma cortisol, late-night salivary cortisol, or the low-dose DST (using 1 mg dexamethasone for the overnight test or 0.5 mg/6 hr for the classic 2-day study). However, because these tests cannot determine the etiology of Cushing syndrome, other tests and procedures must be subsequently employed. Such tests can include any of the following: plasma ACTH via immunoradiometric assay (IRMA) or radioimmunoassay (RIA); adrenal vein catheterization; metyrapone stimulation test; adrenal, chest, or abdominal computed tomography (CT); CRH stimulation test; inferior petrosal sinus sampling (IPSS); jugular venous sampling (JVS); cavernous sinus sampling; and pituitary magnetic resonance imaging (MRI). High-dose DST has been used in the past but is no longer recommended due to its poor specificity and limited diagnostic value. Other possible tests and procedures include insulin-induced hypoglycemia, somatostatin receptor scintigraphy, the desmopressin stimulation test, the naloxone CRH stimulation test, the loperamide test, the hexarelin stimulation test, and radionuclide imaging.[5,6,8,15-20] Table 97-3 summarizes the findings from some of the tests used to diagnose Cushing syndrome.

TABLE 97-3

Summary of Tests Used to Diagnose Cushing Syndrome

Test	Normal	Hyperplasia	Adenoma	Carcinoma
Plasma				
Cortisol (μg/dL or nmol/L, in brackets; for am/pm)	5-25/5-15 (140-690/140-415)	↑/↑↑	↑↑/↑↑	↑↑↑/↑↑↑
After low-dose DST	↓	↔	↔	↔
After high-dose DST	↓	↓/↔	↔	↔
ACTH (pg/mL or pmol/L, in brackets)	6-76 (1.3-17)	↑↑	↓	↓
Urine				
Cortisol (μg/24 hours or nmol/day, in brackets)	20-90 (55-250)	↑↑	↑↑	↑↑↑
Saliva				
Cortisol (μg/dL or nmol/L), PM)	Assay-dependent	↑↑	↑↑	↑↑↑

Data from Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory reference values. N Engl J Med. 2004;351(15):1548–1563.

Elevated UFC concentrations are highly suggestive of Cushing syndrome, especially values fourfold greater than the upper limit of normal.[3,17] In contrast to plasma measurements of cortisol, UFC measures only unbound cortisol. Consequently, the UFC test is unaffected by conditions and medications that alter CBG levels. Normal reference values for UFC are 10 to 60 μg per 24-hour period (30-170 nmol/day). A two- to threefold increase in urine cortisol is not uncommon in the patient with hyperfunction of the adrenal gland. Starvation, hydration from water loading (≥5 L/day), alcoholism, and acute stress are all capable of elevating urine cortisol concentrations. Likewise, elevated UFC results can occur during therapy with carbamazepine, fenofibrate, and topical steroids depending on the type of UFC test. Conversely, renal impairment (creatinine clearance [CrCl] of <60 mL/min [1.0 mL/s]) can falsely lower UFC concentrations. Because other pathologic conditions can increase the amount of free cortisol, additional tests may be warranted to confirm the diagnosis, or the diagnostic evaluation should be repeated when the acute stress has resolved. Of all urinary measures, UFC is the most useful assessment for patients with suspected Cushing syndrome.[8,17,19]

In healthy individuals, cortisol release follows a circadian rhythm whereby serum cortisol concentration peaks around 8:00 am and thereafter declines by 60% to 80%, reaching a nadir between 1:00 and 3:00 am. This rhythm is lost in the patient with Cushing syndrome. Although many patients with

Cushing syndrome will have serum cortisol values in the high normal range if the serum is assayed in the morning, only 3.4% will have normal values if measured late at night.[14] Thus, a midnight serum cortisol greater than 7.5 µg/dL (210 nmol/L; >1.8 µg/dL [50 nmol/L] if the patient is sleeping) is a highly sensitive assay for Cushing syndrome. However, this test is cumbersome and rarely recommended because it requires that patients be admitted for more than 48 hours to avoid false-positive responses secondary to the stress of hospitalization. An alternative assay is the measurement of late-night salivary cortisol. Salivary cortisol is highly correlated with free serum cortisol and independent of salivary flow rates. Moreover, salivary cortisol concentration reflects changes in serum cortisol within minutes. Salivary cortisol can be considered an acceptable alternative to UFC because of its convenience, stability (1 week), accuracy, and reproducibility. Unfortunately, normal reference ranges are assay-dependent, and cutoff points vary among institutions.[21,22]

In the overnight DST, 1 mg of dexamethasone is administered at 11:00 pm. The following morning at 8:00 am fasting plasma cortisol is obtained for analysis. This supraphysiologic dose of dexamethasone suppresses ACTH stimulation and cortisol production in healthy individuals. In contrast, the negative feedback loop is ineffective in patients with Cushing syndrome who generally exhibit a morning cortisol concentration above 5 µg/dL (140 nmol/L). Some patients with Cushing syndrome administered the overnight DST can slightly suppress cortisol and using a 1.8 µg/dL (50 nmol/L) threshold can increase sensitivity, but with reduced specificity.[23] Therefore, the overnight DST is useful only as a screening tool for Cushing syndrome. Drugs that induce or inhibit CYP3A4 metabolism can significantly alter dexamethasone concentration, increasing the likelihood of false-positive and false-negative DSTs. Concurrent measurements of dexamethasone concentration with cortisol may improve the accuracy of testing for patients on CYP3A4-modifying drugs, although dexamethasone assays are not widely available. Also noteworthy, pregnancy and estrogen use (including oral contraceptives) increase CBG levels and frequently elicit false-positive results.[17] Consequently, UFC testing is preferred over DST in these patient populations.

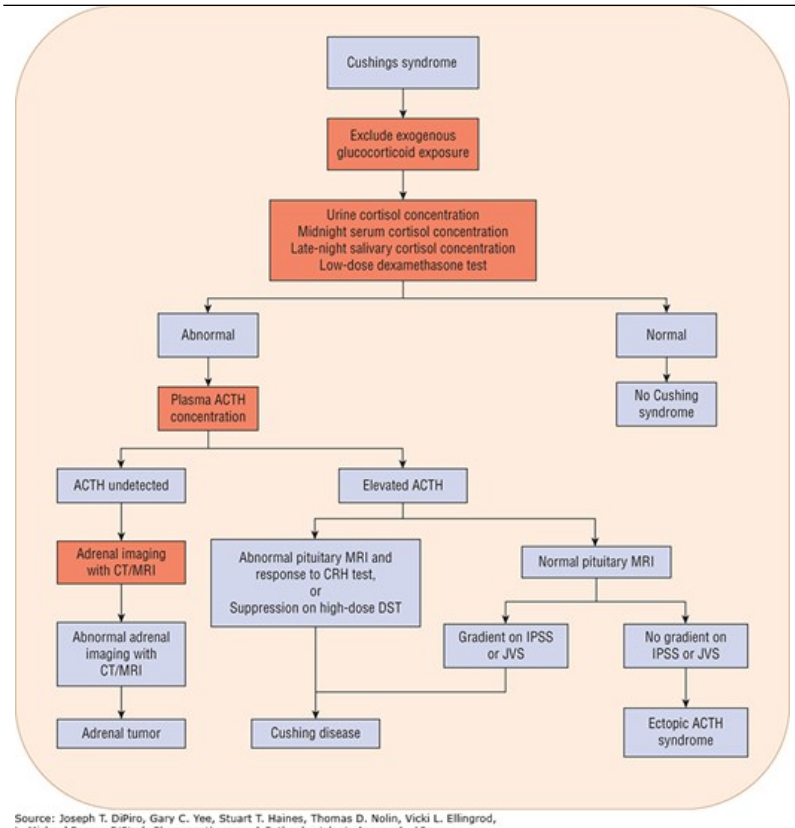
The first test used to determine the etiology of Cushing syndrome is the plasma ACTH test. Plasma ACTH concentrations can be measured via RIA or IRMA.[16] In ACTH-dependent Cushing syndrome, ACTH can be normal or elevated. Very high levels of ACTH favor ectopic production. In contrast, ACTH values generally are low (<5 pg/mL [1.1 pmol/L]) in ACTH-independent (adrenal) Cushing syndrome. Furthermore, ACTH levels can appear artificially low in some ectopic ACTH-producing tumors because ACTH can be secreted as an active prohormone that is not detected by the assay.

IPSS offers the highest sensitivity and specificity of any test in differentiating the etiology of Cushing syndrome. This technique requires catheterization of both petrosal sinuses with serial measurements of ACTH in each sinus and a peripheral vein after administration of CRH. A central-to-peripheral ACTH gradient is diagnostic for Cushing disease, whereas no gradient indicates ectopic ACTH production. Complications, such as venous thromboembolism, brain stem vascular damage, high cost, and technical expertise can limit the use of this test.[16] JVS uses the same concept as IPSS, is less invasive, and produces fewer complications; however, sensitivity is compromised.

Abnormal adrenal anatomy is effectively identified using high-resolution CT scanning and MRI.[24] Nodules as small as 1 to 1.5 cm on the adrenal cortex are easily identified by CT. With the use of thin-section scanning, nodules as small as 3 to 5 mm can be visualized.[25] Importantly, adrenal incidentalomas (masses observed incidentally on imaging) are prevalent in 5% to 10% of the general population. These masses may be functional (secreting), requiring intervention, or nonfunctional (nonsecreting), requiring only periodic observation. For this reason, abnormal imaging results alone are insufficient to conclusively diagnose adrenal disease. Nonadrenal imaging studies may be useful for identifying ectopic sources of ACTH secretion in patients for whom IPSS has ruled out Cushing disease.

FIGURE 97-4

Algorithm for diagnosing Cushing syndrome. (ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CT, computed tomography; DST, dexamethasone suppression test; IPSS, inferior petrosal sinus sampling; JVS, jugular venous sampling; MRI, magnetic resonance imaging.)



3 If left untreated, Cushing syndrome is associated with high morbidity and mortality due to hypertension, diabetes mellitus, cardiovascular disease, and electrolyte abnormalities. On average, patients with Cushing syndrome live only 4 to 5 years following initial diagnosis. The desired outcomes of treatment are to limit such detrimental outcomes and return the patient to a normal functional state by removing the source of hypercortisolism while minimizing pituitary or adrenal deficiencies.

4 The treatment of choice for both ACTH-dependent and ACTH-independent Cushing syndrome is surgical resection of any offending tumors.[3,15] Pharmacologic treatment options which target the etiology of the disease are generally reserved as second-line treatment for those patients who are not surgical candidates (Table 97-4).[3,26-29] Pharmacotherapy may also be used preoperatively or as adjunctive therapy in the postoperative period awaiting a response. Rarely, pharmacotherapy is used as a palliative treatment when surgery is not indicated.

TABLE 97-4

Possible Treatment Options in Cushing Syndrome Based on Etiology

	Treatment	
Etiology	Non-pharmacologic	Pharmacologic
Ectopic ACTH syndrome	Surgery, chemotherapy, irradiation	Metyrapone Ketoconazole
Pituitary-dependent	Surgery, irradiation	Mitotane Metyrapone Mifepristone Cabergoline Pasireotide
Adrenal adenoma	Surgery, postoperative replacement	Ketoconazole
Adrenal carcinoma	Surgery	Mitotane

Non-Pharmacologic Therapy

Pituitary Adenoma

The treatment of choice for Cushing disease is transsphenoidal resection of the pituitary tumor.[3,15,29-31] The advantages of this procedure include preservation of pituitary function, low complication rate, and high clinical improvement rate. The overall cure rate of histologically proven microadenomas (tumor diameter <10 mm) approaches 90%, whereas remission rates for macroadenomas (tumor diameter ≥10 mm) generally do not exceed 65%.

For persistent disease following transsphenoidal surgery or when tumor-specific surgery is not possible, several second-line treatment options are available and should be tailored toward the individual patient.[29] In the case of persistent disease following transsphenoidal surgery, repeat surgery may be performed, particularly in patients with evidence of incomplete resection or pituitary lesion on imaging.[29] Although overall remission rates are lower with subsequent procedures, remission can be achieved rapidly when compared to alternative second-line treatments.[29] Alternatively, radiotherapy may be preferred for tumors invading the dura or cavernous sinus because these tumors respond poorly to surgical intervention.[32] Radiotherapy provides clinical improvement in approximately 50% of patients within 3 to 5 years, but increases the risk for pituitary-dependent hormone deficiencies (hypopituitarism).

Adrenal Adenoma

Laparoscopic adrenalectomy is often preferred in patients with unilateral adrenal adenomas for whom transsphenoidal surgery and pituitary radiotherapy have failed or cannot be used.[3,15,30] Bilateral adrenalectomy rapidly reverses hypercortisolism. However, patients can develop Nelson syndrome, an aggressive pituitary tumor that secretes high quantities of ACTH, which causes hyperpigmentation. Because Nelson syndrome occurs in as many as 30% of bilateral adrenalectomy cases, patients should undergo regular MRI scans and ACTH level assessments. Additionally, these patients require lifelong glucocorticoid and mineralocorticoid supplementation.

Surgical resection of benign adrenal adenoma is associated with relatively few side effects and a high cure rate (95%). The contralateral gland in the patient with adrenal adenoma is usually atrophic; therefore, steroid replacement is needed both perioperatively and postoperatively. Table 97-5

outlines an approach to steroid replacement for three separate routes of hydrocortisone. Therapy should be continued for 6 to 12 months following surgery. Before replacement therapy is discontinued, recovery of the adrenal axis can be assessed by measuring the morning (8:00 am) cortisol concentration. The cortisol concentration should exceed 20 µg/dL (550 nmol/L) before discontinuing exogenous steroids.[11]

TABLE 97-5

Alternative Steroid Replacement Regimens in the Adrenal Adenoma Patient

	Hydrocortisone Dose (mg)		
Time	IV	IM	po
Operation day	300	50 before surgery and 50 after surgery	
Postoperative day 1	200	50 every 12 hours	
Postoperative day 2	150	50 every 12 hours	
Postoperative day 3	100	50 every 12 hours	
Postoperative day 4		50 every 12 hours	25 every 6 hours
Postoperative day 5		25 every 12 hours	25 every 6 hours[a]
Postoperative day 7			25 every 6 hours
Postoperative days 8-10			25 every 8 hours
Postoperative days 11-20			25 every 12 hours
Postoperative days 21+			20 at 8:00 am
			10 at 4:00 pm

(PO, by mouth/orally)

[a]Add fludrocortisone 0.05-2 mg orally once daily starting on postoperative day 5. Adjust dose based on blood pressure, body weight, and serum electrolytes.

Adrenal Carcinoma

Unlike the benign adenoma patient, those with adrenal carcinoma generally have an unfavorable outcome with surgical resection.[15] Often the complete tumor cannot be excised, leaving the patient with some degree of symptoms and extra-adrenal involvement. Radiotherapy can be used if metastases are discovered. In a patient with adrenal carcinoma who is not a surgical candidate, the focus of treatment is on palliative pharmacologic intervention.

Mitotane may be used in inoperable functional and nonfunctional adrenal carcinoma or as adjuvant therapy in surgical patients with a high risk of relapse and may prolong survival by 2 to 3 years.[33] However, mitotane induces tumor regression in fewer than 20% of patients.[34] Metyrapone and ketoconazole can be given as adjunctive treatment to attempt control of steroid hypersecretion. 5-Fluorouracil also has been used in combination therapy.

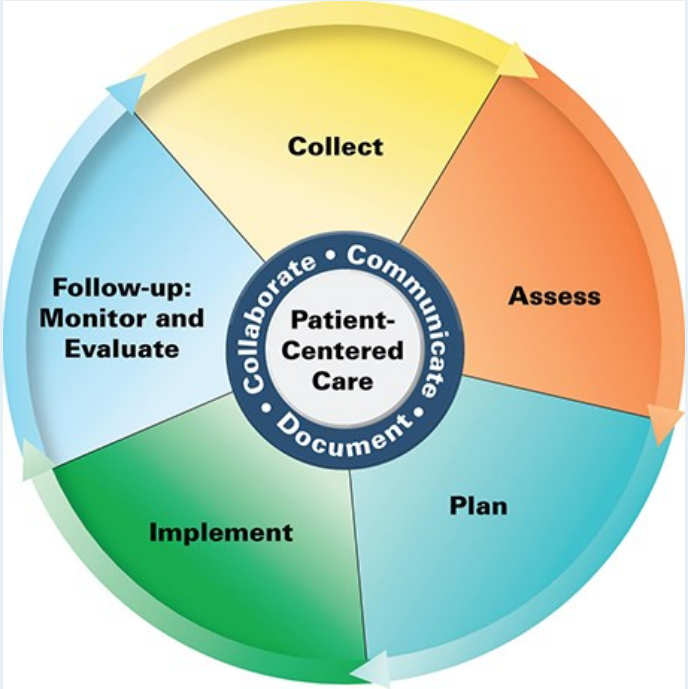
In ectopic ACTH syndrome, ACTH-secreting tumors may exist in a variety of sites, including thymic, pulmonary, appendiceal, pancreatic, and thyroid tissues. Locating these sites is often difficult, but essential for determining an appropriate treatment strategy. Surgical resection is the most effective treatment option for these patients, but only approximately 10% to 30% of patients are cured following surgery due to high rates of metastatic disease or occult tumors. The remaining 70% to 90% receive postoperative medication.

Pharmacologic management with steroidogenesis inhibitors is effective in patients with ectopic ACTH syndrome and may be used as primary treatment in patients with occult or metastatic ectopic ACTH syndrome.[29] Mitotane has been used in this setting; however, its side-effect profile generally limits its use. Mifepristone and somatostatin analogs also have been reported to reduce the clinical signs of ectopic ACTH syndrome.[35]

Additional tumor-directed therapy can include systemic chemotherapy, interferon α, chemoembolization, radiofrequency ablation, and radiation therapy.[32] If all else fails, bilateral adrenalectomy can prevent the downstream effects (eg, steroidogenesis) of high levels of tumor ACTH secretion.

PATIENT CARE PROCESS

Patient Care Process for Cushing Syndrome



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use)
- Iatrogenic causes of Cushing syndrome: current medications including corticosteroids (all routes, past and present), medroxyprogesterone acetate, megestrol acetate, gamma-hydroxybutyic acid, CYP3A4 inhibitors, and inducers
- Objective data
    - Blood pressure, heart rate, body mass index

- Test for hypercortisolism: 24-hour UFC, midnight plasma cortisol, late-night salivary cortisol, or low-dose DST
- Follow-up diagnostic tests to differentiate etiologies (see Fig. 97-4)

Assess

- Presence of Cushing syndrome complications:
  - Metabolic: impaired glucose metabolism, dyslipidemia
  - Cardiovascular: hypertension, vascular damage, thrombosis, hypokalemia
  - Immunologic: bacterial, fungal, and viral infections; rebound autoimmunity Musculoskeletal: osteopenia/osteoporosis, myopathy
  - Neuropsychiatric: depression, anxiety, bipolar disorder, lethargy
  - Reproductive: decreased libido, hypogonadism (men), menstrual irregularity (women)
  - Dermatologic: hirsutism, alopecia, hyperhidrosis
- Physical exam: Peripheral obesity, fat accumulation (Buffalo Hump), rounded face (moon face), striae, ecchymosis, hyperpigmentation, acanthosis nigricans, acne, and thin skin
- Current medications that may contribute to or worsen Cushing syndrome
- Results of follow-up diagnostic testing for etiology (see Fig. 97-4 and Tables 97-2 and 97-3)
- Ability/willingness to pursue surgical/chemotherapeutic (if indicated) versus medical management

Plan*

- Ensure proper administration of necessary corticosteroid therapy; discontinue unnecessary corticosteroid therapy, with taper if HPA axis integrity is suspect
- Nondrug options for endogenous Cushing syndrome, depending on etiology: surgery, chemotherapy, irradiation, postoperative steroid replacement (see Table 97-4)
- Steroid replacement regimens postoperatively for patients with adrenal adenomas (see Table 97-5)
- Medical management when surgery is not possible or against patient wishes (see Tables 97-6 and 97-7 for specific drugs, dose, route, frequency, adverse effects, and monitoring parameters)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, invasive procedures, drug-specific information) and specialist referral when appropriate (eg, endocrinologist)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up for monitoring

Follow-up: Monitor and Evaluate

- Clinical response, including resolution of signs/symptoms

- Treatment-emergent adverse effects (eg, adrenal insufficiency [all], medication-specific adverse effects)
- Monitoring parameters including efficacy (eg, UFC) and safety (eg, ECG, liver function, electrolytes, A1c)
- Frequency and timing of follow-up for specific agents (see Table 97-7 and text for agent-specific monitoring)

Collaborate with patient, caregivers, and other healthcare professionals.

Pharmacologic Therapy

5 Pharmacotherapy of Cushing syndrome can be divided into four categories based on the anatomic site of action: (1) steroidogenesis inhibitors, (2) adrenolytic agents, (3) neuromodulators of ACTH release, and (4) glucocorticoid-receptor blocking agents.[26,27] Dosing and monitoring parameters can be found in Table 97-6 and Table 97-7, respectively.[3,28,29]

Several factors may limit the ability to personalize pharmacotherapy in patients with Cushing syndrome. First, few rigorous studies have compared the various pharmacologic options used in Cushing syndrome. Apart from the benefits seen with pasireotide in patients with modestly elevated UFC and the use of mifepristone in patients with concomitant hyperglycemia, data are limited in terms of clinical predictors of disease response to these agents. Second, virtually nothing is known of the pharmacogenomic predictors of individual patient response in these disease states. Finally, because most agents are used off-label, scarce data exist on agent-specific pharmacokinetic parameters in this patient population.

TABLE 97-6

Drug Dosing in the Treatment of Cushing Syndrome

Drug	Initial Dose	Usual Range	Special Populations	Comments
Cabergoline	0.5 mg once weekly	0.5-7 mg once weekly		Maximum: 7 mg/week
Etomidate	0.03 mg/kg IV bolus	0.1-0.3 mg/kg/hr infusion		Maximum: 0.3 mg/kg/hr infusion; titrate based on serum cortisol concentration
Ketoconazole	200 mg once or twice a day	200-1,200 mg/day, divided twice a day	Contraindicated in patients with hepatic disease	Maximum: 1,600 mg/day; CYP3A4 substrate and inhibitor (strong)
Metyrapone	0.5-1 g/day, divided every 4-6 hours	1-2 g/day, divided every 4-6 hours		Maximum: 6 g/day; CYP3A4 inducer
Mifepristone	300 mg once daily, increased by 300 mg/day every 2-4 weeks	600-1,200 mg/day	Do not exceed 600 mg/day in mild-to-moderate hepatic impairment; avoid in severe hepatic impairment. Do not exceed 600 mg/day in renal impairment	Maximum: 1,200 mg/day not to exceed 20 mg/kg/day
Mitotane	0.5-1 g/day, increased by 0.5-1 g/day every 1-4 weeks	1-4 g/day		Maximum: 12 g/day (most patients unable to tolerate >8 g/day). Take with food to decrease GI effects
Osilodrostat	2 mg twice daily	2-7 mg twice daily	Moderate hepatic impairment: 1 mg twice daily; Severe hepatic impairment: 1 mg once daily in the evening	Comments: Maximum 60 mg/day
Pasireotide	0.6-0.9 mg twice daily	0.3-0.9 mg twice daily	Reduce dose in hepatic impairment	Maximum: 1.8 mg/day

GI, gastrointestinal.

TABLE 97-7

Drug Monitoring in the Treatment of Cushing Syndrome

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Cabergoline	Nausea, dizziness, headache, nasal congestion, constipation, psychiatric symptoms, valvulopathy	Echocardiogram	
Etomidate	Sedation, pain at the injection site, hypotension, myoclonus, nausea, vomiting	Frequent sedation scoring initially, serum potassium, serum cortisol	
Ketoconazole	GI upset, dermatologic reactions; elevated hepatic transaminases, hepatotoxicity	Liver function tests, including ALT/AST, total bilirubin, ALP, prothrombin time, and INR testing	Approximately 10% will experience reversible LFT elevations
Metyrapone	Androgenic effects (hirsutism, acne, etc.), blood pressure and electrolyte abnormalities, nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, allergic rash	Blood pressure, electrolytes	
Mifepristone	Hypokalemia, nausea, fatigue, headache, peripheral edema, dizziness, endometrial hyperplasia	Serum potassium, pregnancy testing, pelvic ultrasound	Abortifacient; rule out pregnancy in women of childbearing potential
Mitotane	GI upset, nausea, diarrhea, lethargy, somnolence, CNS disturbances	UFC and urinary steroid production, serum potassium	GI upset in up to 80%; GI and CNS effects appear to be dose-dependent
Pasireotide	Nausea, diarrhea, cholelithiasis, increased hepatic transaminases, hyperglycemia, sinus bradycardia, QT prolongation	Serum glucose, serum potassium, hemoglobin A1c, liver function tests, UFC, thyroid function, heart rate, ECG	Only available as a subcutaneous injection; expensive

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; FDA, Food and Drug Administration; INR, international normalized ratio; LFT, liver function tests; GI, gastrointestinal; ECG, electrocardiogram; UFC, urinary free cortisol.

With these limitations in mind, drug selection is determined according to the etiology of Cushing syndrome, individual patient factors, drug-drug interactions, and cost. Once the etiology has been correctly identified, patient sex and gender should be considered since some pharmacologic options (steroidogenesis inhibitors in particular) used in Cushing syndrome affect the sex hormones. Specifically, metyrapone is a clear second choice in women due to a high incidence of hirsutism, whereas ketoconazole may be a secondary choice in men due to drug-induced gynecomastia and hypogonadism. During pregnancy, metyrapone is commonly used, while mifepristone must be avoided. Additionally, women desiring pregnancy within the next five years should avoid mitotane as this agent is stored in adipose tissue for up to several years following discontinuation. Preexisting medication profiles should also be considered since many of the pharmacologic options can inhibit (eg, ketoconazole) or induce (eg, metyrapone) important CYP isoenzymes such as 3A4.

Ultimately, pharmacotherapy is guided by patient response and several agents may need to be sequentially tried to elicit a substantial response. Combination therapy may be more effective and better tolerated than monotherapy in some patients, but studies involving multi-drug regimens are lacking.

Steroidogenesis Inhibitors

As their name implies, steroidogenesis inhibitors block the production of cortisol. This class includes metyrapone, ketoconazole, etomidate, and

osilodrostat. Metyrapone inhibits 11β-hydroxylase, the enzyme responsible for converting 11-deoxycortisol to cortisol. Following administration, a sudden decrease in cortisol concentration occurs within hours and prompts a compensatory rise in plasma ACTH concentrations. As ACTH increases and blockage of cortisol synthesis persists, adrenal steroidogenesis efforts are shunted toward androgen production. Consequently, metyrapone is associated with significant androgenic side effects, including hirsutism and increased acne, making it less ideal for women. In addition, metyrapone blocks aldosterone synthesis and causes the accumulation of aldosterone precursors, which exhibit weak mineralocorticoid activity. Blood pressure and electrolyte perturbations can ensue, depending on the level of circulating 11-deoxycortisol and the degree of aldosterone inhibition. Additional adverse effects, including nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, and allergic rash, have been reported following administration, but are often signs of overtreatment.[26,27,30]

The imidazole derivative antifungal, ketoconazole, effectively inhibits steroidogenesis via multiple mechanisms when used in large doses. In contrast to the quick onset of metyrapone, the benefits of ketoconazole therapy are achieved only after several weeks of therapy. In addition to lowering serum cortisol levels, ketoconazole exhibits antiandrogenic activity attributable to its inhibition of multiple CYP enzymes as well as 11β-hydroxylase and 17α-hydroxylase.[26] This activity may be beneficial in women with Cushing syndrome but can cause gynecomastia and hypogonadism in men. Sustained therapy with ketoconazole also imparts beneficial effects on serum cholesterol profiles, including lowering total and low-density lipoprotein (LDL) cholesterol levels. Ketoconazole induces a reversible elevation of hepatic transaminases in approximately 10% of patients.[36] However, concerns have been raised over the risk of severe hepatotoxicity associated with ketoconazole use. In July 2013, the US Food and Drug Administration (FDA) significantly changed the labeling of oral ketoconazole, removing various indications for fungal infections and recommending that oral ketoconazole not be used as first-line therapy for fungal infections. Similarly, the European Medicines Agency has recommended the complete removal of oral ketoconazole from European Union markets. These changes were based largely on data in patients with fungal infections, who require lower doses of ketoconazole. However, few data are available on the incidence of severe hepatotoxicity with ketoconazole at the higher doses used in Cushing syndrome. Consequently, monitoring during treatment with ketoconazole should include liver function at baseline, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), prothrombin time, and international normalized ratio (INR) testing, according to FDA recommendations. In addition, weekly monitoring of serum ALT should be continued throughout therapy with ketoconazole. In general, ketoconazole should be avoided in patients with preexisting hepatic disease. Additional common adverse effects include gastrointestinal (GI) discomfort and dermatologic reactions.

Ketoconazole may be used concomitantly with metyrapone to achieve synergistic reductions in cortisol levels. Because these drugs differ in their onset of action, coadministration allows for more complete suppression of cortisol synthesis. Moreover, the antiandrogenic actions of ketoconazole therapy may offset the androgenic potential of metyrapone, thus attenuating a major limitation of metyrapone monotherapy.

The anesthetic etomidate is an imidazole derivative similar to ketoconazole that inhibits 11β-hydroxylase.[26] Inhibition of aldosterone synthase and antiproliferative effects on adrenal cortical cells may also play a role.[37] Etomidate is available only in a parenteral formulation and is therefore limited to patients with acute hypercortisolemia requiring emergency treatment or in preparation for surgery. Low doses of etomidate are often sufficient to suppress cortisol synthesis, thus potentially avoiding some of the adverse effects observed with higher doses used in anesthesia. However, close monitoring is recommended to avoid excess sedation with this agent.[37] Frequent monitoring of serum cortisol is also advised to prevent hypocortisolemia. Replacement corticosteroid doses may be necessary if a complete blockade of cortisol is desired.

Osilodrostat prevents cortisol synthesis via inhibition of 11β-hydroxylase and is indicated for treating patients with Cushing disease who are either not candidates for surgical therapy or in whom symptoms persist after surgery. Osilodrostat is available as an oral tablet administered twice daily, with or without food. Electrolyte imbalances, namely hypokalemia and hypomagnesemia, should be corrected prior to use, and an ECG should be obtained at baseline and again one week after treatment initiation to monitor possible QTc prolongation. Adverse effects are similar to other 11β-hydroxylase inhibitors, including hypocortisolism, QTc prolongation, nausea, and headache.

Adrenolytic Agents

Mitotane is a cytotoxic drug that structurally resembles the insecticide dichlorodiphenyltrichloroethane (DDT). Mitotane inhibits the 11-hydroxylation of 11-desoxycortisol and 11-desoxycorticosterone in the adrenal cortex, resulting in an inhibition of cortisol and corticosterone synthesis. Similar to ketoconazole, mitotane takes weeks to months to exert beneficial effects. Sustained cortisol suppression occurs in most patients (~80%) and may persist following discontinuation of therapy in up to one-third of patients. Because of its cytotoxic nature, 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.[28,29]

Importantly, mitotane can induce significant neurologic and GI side effects and patients should be monitored carefully or hospitalized when initiating therapy. Nausea and diarrhea are common adverse effects that occur at doses greater than 2 g/day and can be avoided by gradually increasing the dose and/or administering the agent with food. Most patients are unable to tolerate doses exceeding 8 g/day. Approximately 80% of patients treated with mitotane develop lethargy and somnolence, and other central nervous system (CNS) adverse drug reactions occur in approximately 40% of patients. Furthermore, significant but reversible hypercholesterolemia and prolongation of bleeding times can result from mitotane use.[26,27] Mitotane increases production of CBG resulting in elevated plasma cortisol measurements; thus, UFC and urinary steroid production should be monitored to assess response to therapy.[26] If necessary, steroid replacement therapy can be given. However, because mitotane also increases extra-adrenal metabolism of exogenously administered corticosteroids (especially hydrocortisone), higher steroid replacement doses may be required. In select patients, supplemental androgen therapy also may be necessary.

Neuromodulatory Agents

Pituitary secretion of ACTH is normally mediated by various neurotransmitters, including serotonin, γ-aminobutyric acid (GABA), acetylcholine, and the catecholamines. Although ACTH-secreting pituitary tumors (Cushing disease) self-regulate ACTH production to some degree, these neurotransmitters are still capable of promoting pituitary ACTH production. Consequently, agents that target these neurotransmitters have been proposed for the treatment of Cushing disease. Such agents include cyproheptadine, ritanserin, ketanserin, bromocriptine, cabergoline, valproic acid, octreotide, lanreotide, pasireotide, rosiglitazone, and tretinoin. However, with the exception of pasireotide, none of these drugs have demonstrated consistent clinical efficacy in the treatment of Cushing disease.

Cyproheptadine, a nonselective serotonin-receptor antagonist and anticholinergic drug, can decrease ACTH secretion in some patients with Cushing disease. However, side effects, including sedation and weight gain, significantly limit the use of this drug. Likewise, selective serotonin type 2-receptor antagonists, including ritanserin and ketanserin, have demonstrated limited efficacy. Owing to their poor efficacy and high relapse rates, these drugs should be avoided except in nonsurgical candidates refractory to more conventional treatments.

Dopamine D_2-receptor agonists, including bromocriptine and cabergoline, initially reduce ACTH secretion in as many as half of all patients with Cushing disease. This action occurs through the activation of inhibitory D_2 receptors that are expressed in approximately 80% of pituitary adenomas.[38] Reductions in ACTH levels are often minor and rarely sustained with long-term bromocriptine therapy. Cabergoline exhibits a higher specificity and affinity for D_2 receptors as well as a prolonged half-life compared with bromocriptine. These differences may explain the greater response rates observed with cabergoline monotherapy; however, a sustained response occurs in only 30% to 40% of patients.[39,40] Although generally well-tolerated, side effects associated with cabergoline include nausea, orthostasis, headache, nasal congestion, constipation, nightmares, vivid dreams, and psychosis. The risk of cabergoline-associated cardiac valvulopathy (observed with higher doses used to treat Parkinson disease) has not been well-studied in lower doses typically used for the treatment of Cushing disease.[41]

The somatostatin analogs octreotide and lanreotide generally are ineffective in reducing ACTH secretion in Cushing disease. These two agents primarily target somatostatin receptor subtype 2 (sst_2), whereas pituitary adenomas predominantly express sst_5. Pasireotide, a somatostatin analog, exhibits a high affinity for sst_1, sst_2, sst_3, and, especially, sst_5 receptor subtypes. In a phase 3 study of 162 adults with Cushing disease and an elevated UFC, pasireotide administered at 600 or 900 µg injected subcutaneously twice daily reduced the median UFC by 50% by month two; levels remained stable for the duration of the 12-month study.[42] Pasireotide is especially effective at normalizing UFC concentrations in patients whose baseline UFC is less than five times the upper limit of normal. Clinical signs and symptoms of Cushing disease are also improved as are blood pressure, weight, LDL cholesterol, and quality of life. Side effects are mostly GI in nature, although 50% to 70% of subjects experience an adverse event related to hyperglycemia; preexisting diabetes mellitus or impaired glucose tolerance increases the risk for these events. Notably, pasireotide increases glycated hemoglobin A1c by an average of 1.4% (0.014; 15 mmol/mol Hb) at 6 months and this effect may be sustained with long-term therapy,[43] likely due to impaired insulin secretion.[44]

Since coexpression of D_2 and sst_5 receptors is common in adrenocorticotropin-secreting adenomas, the combination of pasireotide and cabergoline may produce synergistic effects in reducing cortisol levels.[3] Limited data suggest that step-wise addition of cabergoline and ketoconazole in patients

unresponsive to pasireotide may achieve normalization of UFC in the majority of patients; however, additional studies are needed to confirm the efficacy of this combination therapy. Potential drug-drug interactions exist with the combination of pasireotide and ketoconazole, and thus, the combination should be used with caution.[43,45,46]

Glucocorticoid-Receptor Blocking Agents

Mifepristone is a potent progesterone- and glucocorticoid-receptor antagonist that inhibits dexamethasone suppression and increases endogenous cortisol and ACTH levels in normal subjects.[26,30] Clinical experience and trial data in Cushing syndrome suggest that mifepristone is highly effective in reversing the manifestation of hypercortisolism, including hyperglycemia, hypertension, and weight gain.[47] Consequently, mifepristone has an FDA-approved indication for treatment of endogenous Cushing syndrome in patients who have diabetes mellitus or glucose intolerance, and who are not eligible for or have had poor response to surgery. However, because of its novel site of action, mifepristone induces a compensatory rise in ACTH and cortisol. Consequently, efficacy and toxicity monitoring must rely on clinical signs rather than laboratory assessments. Common adverse effects of mifepristone include fatigue, nausea, headache, arthralgia, peripheral edema, endometrial thickening (with or without vaginal bleeding), and significant reductions in serum potassium. Oral potassium supplementation or spironolactone can be effective in mitigating the latter adverse effect, although high doses may be required.[47]

Close monitoring of 24-hour UFC and serum cortisol is essential to detect treatment-induced adrenal insufficiency. Steroid secretion should be monitored with all of these drugs except mifepristone and steroid replacement given as needed. Whatever the choice, pharmacologic therapy in pituitary-dependent disease is mainly centered around patient stabilization prior to surgery or in patients waiting for potential response to other therapies.

Hyperaldosteronism

Excess aldosterone secretion, hyperaldoteronism, can be the result of either primary or secondary causes.[48-51] In primary hyperaldosteronism (PA), the stimulation for aldosterone secretion arises from within the adrenal gland. Conversely, extra-adrenal stimulation is classified as secondary aldosteronism.

Primary Aldosteronism

Etiology

The most common causes of PA include BAH (65%) and aldosterone-producing adenoma (APA; otherwise known as Conn syndrome) (30%). Rare causes include unilateral (primary) adrenal hyperplasia, adrenal cortex carcinoma, renin-responsive adrenocortical adenoma, and three forms of familial hyperaldosteronism (FH): FH type I, also known as glucocorticoid-remediable aldosteronism (GRA); FH type II, also known as familial occurrence of adenoma or hyperplasia type II; and FH type III.[48,50,51]

CLINICAL PRESENTATION

PA is present in approximately 10% of patients with hypertension and is a leading cause of secondary hypertension and treatment resistant hypertension. The disease is more common in women than in men, and diagnosis usually occurs between the third and sixth decades of life. Signs and symptoms can include arterial hypertension, which is often moderate to severe and resistant to pharmacologic intervention. Many patients also have hypokalemia (10%-40%), muscle weakness, fatigue, and headache. These features are nonspecific and many patients are asymptomatic. Historically, hypokalemia was considered a requisite feature for PA diagnosis; however, normokalemia exists frequently in patients and does not rule out PA. Unexplained new-onset of atrial fibrillation or other arrhythmias may also be indicative of PA.[52]

CLINICAL PRESENTATION: Primary Aldosteronism

Symptoms

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

Signs

- Hypertension
- Tetany/paralysis
- Polydipsia/nocturnal polyuria

Laboratory Tests

- A plasma-aldosterone-concentration–to–plasma-renin-activity (PAC–to–PRA) ratio or aldosterone-to-renin ratio (ARR) greater than 30 ng/dL per ng/(mL·h) (830 pmol/L per mcg/[L·h] and a PAC greater than 15 ng/dL (420 pmol/L) is suggestive of PA.
- Common laboratory findings include suppressed PRA, elevated PAC, hypernatremia (>142 mEq/L [mmol/L]), hypokalemia, hypomagnesemia, elevated bicarbonate concentration (>31 mEq/L [mmol/L]), and glucose intolerance.

Confirmatory Tests

- Oral or IV saline loading, fludrocortisone suppression test (FST), and genetic testing

Diagnosis

Early diagnosis and treatment of PA are essential as patients with PA are at increased risk of adverse cardiovascular outcomes compared to patients with essential hypertension alone.[53] Diagnostic confirmation of PA is obtainable through screening, confirmatory tests, and subtype differentiation (Fig. 97-5). The discovery of the underlying etiology ensures proper treatment. Table 97-8 lists the various abnormalities that must be ruled out when hyperaldosteronism is suspected.

TABLE 97-8

Differential Diagnosis of Primary Aldosteronism

Disease	Plasma Renin Activity	Plasma Aldosterone Concentration	Blood Pressure
Primary aldosteronism	Low	High	High
Edematous disorders	High	High	Normal
Malignant hypertension	High	High	High
Congenital adrenal hyperplasia	Low	Low	High
Cushing syndrome	Low to normal	Low to normal	High
Liddle syndrome	Low	Low	High
Bartter syndrome	High	High	Low to normal
Licorice ingestion	Low	Low	High
Low-renin essential hypertension	Low	Low to normal	High

Initial diagnosis is made by screening patients with suspected PA. Any patient with a blood pressure greater than 150/100 mm Hg measured on three separate days and those meeting the criteria for treatment-resistant hypertension should be screened.[54] 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 less than 40 years, and all patients with hypertension and a first-degree relative diagnosed with PA.

Screening for PA is most often done by using the PAC-to-PRA ratio, otherwise known as the ARR. An elevated ARR is highly suggestive of PA; however, an optimal cutoff ratio remains elusive because testing conditions (posture, time, current drug therapy, recent dietary salt intake), patient characteristics, and assay variability can significantly alter test results.[55] ARR cutoffs of 20 to 40 ng/dL per ng/(mL·h) (550 to 1100 pmol/L per (mcg/[L·h]) with an aldosterone concentration greater than 15 ng/dL (420 pmol/L) are used most often.[49,55–57]

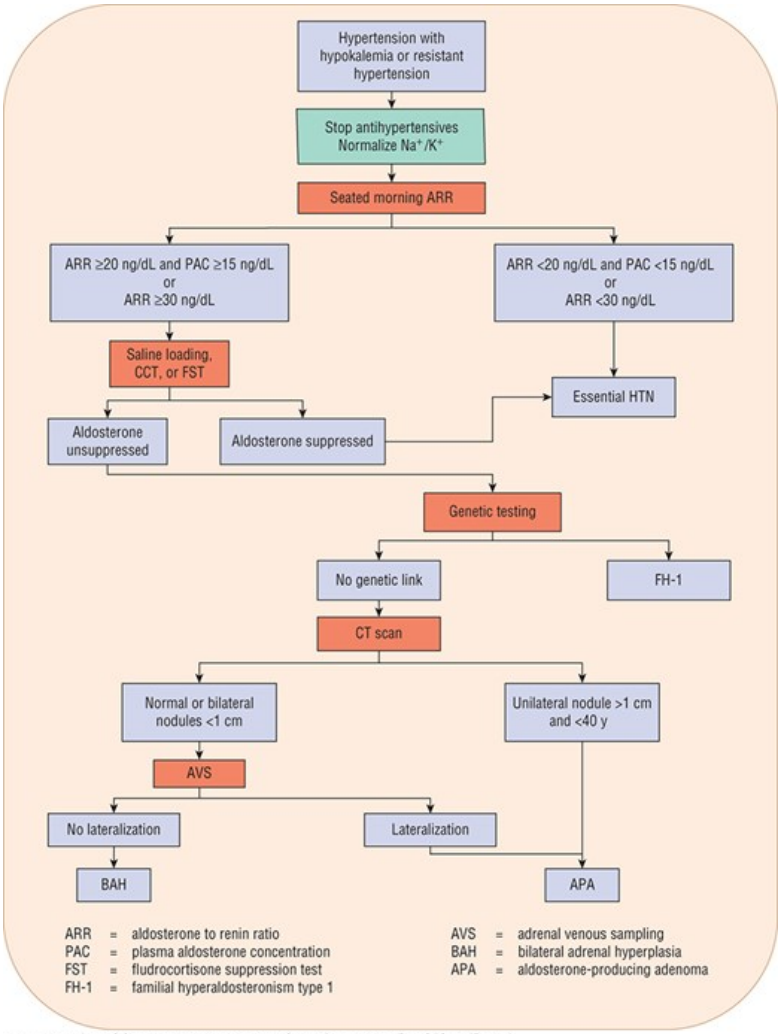
Following a positive ARR screening test, confirmatory testing must be performed to exclude false-positive cases. Confirmatory tests include the oral sodium loading test, saline infusion test (SIT), fludrocortisone suppression test (FST), and the captopril challenge test (CCT). Although individual tests can vary in sensitivity, specificity, and reliability, any test can be used depending on patient- and institution-specific considerations. FST generally is considered the most reliable but requires hospitalization. The SIT and CCT are both accurate alternatives to FST. However, a post-CCT evaluation of PAC is recommended to help interpret results of this confirmatory test.[58] Prior to performing these tests, potassium must be normalized and renin-angiotensin-aldosterone system (RAAS) inhibitors should be temporarily discontinued, if possible. Positive tests indicate autonomous aldosterone secretion under inhibitory pressures and are diagnostic for PA. After diagnosis, patients with confirmed PA before age 20 or with a family history of PA or strokes before age 40 should undergo genetic testing for GRA.[55]

Differentiating between an APA and BAH is imperative to formulate a proper treatment plan. Most adenomas are singular and small (<1 cm) and occur more often in the left adrenal gland than the right. Patients with APA generally have more severe hypertension, more profound hypokalemia, and higher plasma and urinary aldosterone concentrations compared with patients with BAH. Adrenal venous sampling (AVS) provides the most accurate means of differentiating unilateral from bilateral forms of PA. However, AVS is expensive, invasive, and often unavailable. CT scanning can detect most adenomas, although an incidentaloma can occasionally cause confusion. If CT scanning is inconclusive, AVS is performed to characterize lateralization.[49,59-61]

The underlying abnormality in BAH remains a mystery, but some investigators believe that a hormone factor stimulates the zona glomerulosa, resulting in increased sensitivity to angiotensin II. In contrast to those with an APA, patients with BAH are able to maintain control of the renin-angiotensin system, with little effect following doses of ACTH.

FIGURE 97-5

Algorithm for the diagnosis of primary aldosteronism. (ARR, aldosterone-to-renin ratio expressed in ng/dL per ng/(mL·h); HTN, hypertension; PAC, plasma aldosterone concentration [multiply values by 27.74 for units of pmol/L]).



TREATMENT

BAH-Dependent Aldosteronism

Aldosterone-receptor antagonists are the treatment of choice in BAH. Drug dosing and monitoring parameters can be found in Tables 97-9 and 97-10. Spironolactone, a nonselective aldosterone-receptor antagonist, competes with aldosterone for binding at the aldosterone receptor, thus preventing the negative downstream effects of aldosterone-receptor activation. Additionally, spironolactone is capable of inhibiting aldosterone synthesis within the adrenal gland; however, the magnitude of inhibition is relatively small and the effect only occurs above recommended doses.[62] Spironolactone is available in oral form, with most patients responding to doses between 25 and 400 mg/day. The clinician should wait 4 to 8 weeks before reassessing

the patient for urinary electrolytes and blood pressure control. Adverse effects of spironolactone are dose-dependent and include GI discomfort, impotence, gynecomastia, menstrual irregularities, and hyperkalemia. Gynecomastia and menstrual irregularities observed with spironolactone therapy arise from activity at androgen and progesterone receptors and inhibition of testosterone biosynthesis. Additionally, because salicylates increase the renal secretion of canrenone, the active metabolite of spironolactone, patients should be advised to avoid concomitant therapy with salicylates. In patients intolerant of spironolactone, alternative options include eplerenone and amiloride.[50,51,63-65]

TABLE 97-9

Drug Dosing in the Treatment of Hyperaldosteronism

Drug	Initial Dose	Usual Range	Special Populations	Comments
Amiloride	5 mg twice daily	20 mg/day in two divided doses	CrCl 10-50 mL/min (0.17-0.84 mL/s): reduce dose by 50%; CrCl <10 mL/min (0.17 mL/s): CI	Maximum: 30 mg/day
Eplerenone	50 mg once daily	100-300 mg/day in single or divided doses; titrate at 4- to 8-week intervals	CrCl <30 mL/min (0.5 mL/s): CI	Maximum: 300 mg/day
Spironolactone	25 mg once daily	100-400 mg/day in single or divided doses; titrate at 4- to 8-week intervals	CrCl 10-50 mL/min (0.17-0.84 mL/s): extend dosing interval to once daily; CrCl <10 mL/min (0.17 mL/s): CI	Maximum: 400 mg/day

CI, contraindicated; CrCl, creatinine clearance.

TABLE 97-10

Drug Monitoring in the Treatment of Hyperaldosteronism

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Amiloride	Electrolyte abnormalities (hyperkalemia), hypotension, nausea, vomiting, diarrhea, headache	Serum creatinine, serum potassium, blood pressure	Electrolyte abnormalities (hyperkalemia) more pronounced with reduced renal function
Eplerenone	Electrolyte abnormalities (hyperkalemia), hypotension, dizziness, headache; gynecomastia and menstrual irregularities are uncommon	Serum creatinine, serum potassium, blood pressure	Electrolyte abnormalities (hyperkalemia) more pronounced with reduced renal function. CYP3A4 substrate; avoid use with potent CYP3A4 inhibitors
Spironolactone	GI discomfort, impotence, gynecomastia, menstrual irregularities, electrolyte abnormalities (hyperkalemia), hypotension	Serum creatinine, serum potassium, blood pressure	Electrolyte abnormalities (hyperkalemia) more pronounced with reduced renal function

Eplerenone is a selective aldosterone-receptor antagonist with high affinity for the aldosterone receptor and low affinity for androgen and progesterone receptors. Consequently, eplerenone elicits fewer sex steroid–dependent effects than spironolactone. Randomized controlled trial data have been inconclusive with regard to whether eplerenone achieves similar blood pressure reductions to spironolactone and there are limited long-

term data comparing these agents.[66,67] Eplerenone dosing starts at 50 mg daily, with titration to 50 mg twice a day; some patients may require total daily doses as high as 200 to 300 mg.[63] Titration should occur at 4- to 8-week intervals. In addition, eplerenone is a substrate of CYP3A4 and should not be taken with potent CYP3A4 inhibitors. Eplerenone is the preferred aldosterone antagonist during pregnancy since spironolactone can cause ambiguous genitalia in a male fetus.[68]

Amiloride, a potassium-sparing diuretic, is dosed at 5 mg twice a day up to 30 mg/day if necessary. Amiloride is less effective than spironolactone and patients often require additional therapy to adequately control blood pressure. Additional second-line options include calcium channel blockers, ACE inhibitors, and diuretics such as chlorthalidone, although all lack outcome data in PA.[61,64] However, some agents (eg, diuretics, calcium channel blockers) can promote a reactive rise in PRA, ultimately leading to increased aldosterone levels and potentially worsening PA. A prudent strategy would be to use these agents only in combination with RAAS inhibitors to mitigate the downstream aldosterone effects of any increase in PRA.

Initiation of these drugs, particularly spironolactone and eplerenone, should be accompanied by close monitoring of blood pressure. Both agents can cause significant reductions in blood pressure and patients may need to reduce the dose or discontinue other antihypertensive drugs in their regimens.

APA-Dependent Aldosteronism

The treatment of choice for APA-dependent aldosteronism remains laparoscopic resection of the adenoma.[69] Nearly 100% of patients show blood pressure improvement and up to 72% are permanently cured.[65,70] Because APAs are small and often occur in multiples, resection should target the entire adrenal gland. In successful cases, blood pressure control is achieved in one to three months. Medical management with an aldosterone receptor antagonist is often effective in this population if surgery is contraindicated. However, medical management may be significantly more expensive than unilateral resection.

Glucocorticoid-Remediable Aldosteronism

Glucocorticoids are very effective in treating GRA.[32] Low doses of long-acting glucocorticoids are used (0.125-0.5 mg/day of dexamethasone or 2.5-5 mg/day of prednisone) because complete suppression of ACTH-stimulated aldosterone release is unnecessary. If blood pressure fails to normalize with glucocorticoid therapy alone, the addition of spironolactone, eplerenone, or amiloride may help control symptoms.[49]

Secondary Aldosteronism

Secondary aldosteronism results from an appropriate response to excessive stimulation of the zona glomerulosa by an extra-adrenal factor, usually the renin-angiotensin system. Excessive potassium intake can promote aldosterone secretion as well as oral contraceptive use, pregnancy (aldosterone secretion 10 times normal by the third trimester), and menses. Congestive heart failure, cirrhosis, renal artery stenosis, and Bartter syndrome also can lead to elevated aldosterone concentrations.

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

HYPOFUNCTION OF THE ADRENAL GLAND

Hypofunction of the adrenal gland can affect any or all adrenal hormones, depending on the etiology of the disorder. However, hypofunction does not always lead to insufficient production of adrenal hormones. Some types of adrenal hypofunction can lead to excess production of certain hormones.

Addison Disease

7 Primary adrenal insufficiency, or Addison disease, most often involves the destruction of all regions of the adrenal cortex. Deficiencies arise in cortisol, aldosterone, and the various androgens, and levels of CRH and ACTH increase in a compensatory manner. In developed countries, autoimmune dysfunction is responsible for most cases (80%-90%), whereas tuberculosis predominates as the cause in developing countries. Approximately 50% of patients with autoimmune etiologies present with one or more concomitant autoimmune disorders, usually involving other

endocrine organs. Autoimmune thyroid disorders (eg, Hashimoto thyroiditis or Graves' disease) are the most common, but the ovaries, pancreas, parathyroid gland, and organs of the GI system can also be affected. This polyglandular failure syndrome, termed autoimmune polyendocrine syndrome (APS), is associated with the idiopathic etiology only and has not been seen with adrenal insufficiency associated with tuberculosis or other invasive diseases. Medications that inhibit cortisol synthesis (ketoconazole) or accelerate cortisol metabolism (phenytoin, rifampin, phenobarbital) can also cause primary adrenal insufficiency.[71]

8 Secondary insufficiency is characterized by reduced glucocorticoid production secondary to decreased ACTH levels. Low levels of ACTH most commonly result from exogenous steroid use, leading to suppression of the HPA axis and decreased release of ACTH, as well as impaired androgen and cortisol production. These effects occur with oral, inhaled, intranasal, and topical glucocorticoid administration.[72-74] Moreover, mirtazapine and progestins, such as medroxyprogesterone acetate and megestrol acetate, have been reported to induce secondary adrenal insufficiency.[75,76] Chronic suppression also can result in atrophy of the anterior pituitary and hypothalamus, impairing recovery of function if the exogenous steroid is reduced. Endogenous secondary insufficiency can occur with tumor development in the hypothalamic-pituitary region. Secondary disease classically presents with normal concentrations of mineralocorticoids since the zona glomerulosa is controlled by the renin-angiotensin system rather than ACTH levels.

Approximately 90% of the adrenal cortex must be destroyed before the symptoms of adrenal insufficiency become clinically manifest.[77] Etiologies for both primary and secondary insufficiency are listed in Table 97-11. Adrenal hemorrhage can result from multiple etiologies including traumatic shock, coagulopathies, ischemic disorders, and other situations of severe stress, but septicemia is the most common. Symptoms include truncal pain, fever, shaking, chills, hypotension preceding shock, anorexia, headache, vertigo, vomiting, rash, psychiatric symptoms, abdominal rigidity or rebound, and death in 6 to 48 hours if not treated. The most common organisms found on autopsy are *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, Group A *Streptococcus*, and *Haemophilus influenzae*.[77,78]

TABLE 97-11

Etiologies of Primary and Secondary Adrenal Insufficiency

Primary Insufficiency	Secondary Insufficiency
Slow onset	Craniopharyngioma
Acquired immunodeficiency syndrome	Cure of Cushing syndrome
Adrenomyeloneuropathy	Empty sella syndrome
Adrenoleukodystrophy	Tumors of the third ventricle
Amyloidosis	Histiocytosis
Autoimmune adrenalitis[a]	Hypothalamic tumors
Bilateral adrenalectomy	Hypopituitarism
Congenital adrenal hypoplasia	Long-term corticosteroid administration
Hemochromatosis	Lymphocytic hypophysitis
Isolated glucocorticoid deficiency	Pituitary surgery, radiation, or tumor
Metastatic neoplasia	Sarcoidosis
Systemic fungal, bacterial, or viral infections, tuberculosis[b]	Medications—progestins and glucocorticoid discontinuation
Medications—ketoconazole, etomidate, rifampin, phenytoin, phenobarbital	Postpartum pituitary necrosis Necrotic or bleeding pituitary macroadenoma
Fast onset	
Adrenal thrombosis, hemorrhage, sepsis, trauma, or necrosis	Head trauma, lesions of the pituitary stalk, pituitary or adrenal surgery for Cushing syndrome

[a]Approximately 70% of cases.

[b]Approximately 20% of cases.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Adrenal Insufficiency

Symptoms

- Patients commonly complain of weakness, weight loss, GI symptoms, craving for salt, 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 will develop.

Signs

- Increased pigmentation
- Hypotension (postural)
- Fever
- Decreased body hair
- Vitiligo
- Features of hypopituitarism (amenorrhea and cold intolerance)

Laboratory Tests

- The short cosyntropin stimulation test can be used to assess patients suspected of hypercortisolism.

Other Diagnostic Tests

- Other tests include the insulin hypoglycemia test, the metyrapone test, and the CRH stimulation test.

Diagnosis

Distinguishing Addison disease from secondary insufficiency is difficult; however, the following guidelines may be helpful:

1. Hyperpigmentation, commonly found in areas of skin exposed to increased friction, is seen only in Addison disease because of excess secretion of ACTH and other proopiomelanocortin (POMC) peptides that induce melanocyte-stimulating hormone production. Secondary adrenal insufficiency is fundamentally characterized by deficient ACTH and POMC peptide secretion and a correspondingly low level of melanocyte-stimulating hormone production. In fact, some patients with secondary insufficiency may exhibit pale-colored skin secondary to hypopigmentation.
2. Aldosterone secretion usually is preserved in secondary insufficiency.
3. Weight loss, dehydration, hyponatremia, hyperkalemia, and elevated blood urea nitrogen are common in Addison disease.
4. Addison disease will have an abnormal response to the short corticotropin stimulation test. Plasma ACTH levels are usually elevated (400-2,000 pg/mL [88-440 pmol/L]) in primary insufficiency, versus low to normal (5-50 pg/mL [1.1-11 pmol/L]; see Table 97-3) in secondary insufficiency. A normal corticotropin stimulation test does not rule out secondary adrenal insufficiency, particularly in mild cases.

The short corticotropin stimulation test, also known as the cosyntropin stimulation test, can be used to assess patients suspected of hypocortisolism. A 250 µg dose of synthetic ACTH intravenously or intramuscularly to the patient and the serum cortisol is measured at immediately prior to and 30 to 60 minutes after the injection. A resulting cortisol concentration ≥18 µg/dL (500 nmol/L) rules out adrenal insufficiency.[79] Because 250 µg represents a massive supraphysiologic dose, this test can elicit normal, elevated cortisol responses in some cases of mild secondary insufficiency. Thus, some suggest that higher cutoff values (≥22 µg/dL [610 nmol/L]) should be used to prevent false-negative test results.[80] Alternatively, a low-dose

corticotropin stimulation test, using 1 µg of synthetic ACTH, can achieve similar results to the standard dose test. Neither test is very effective in ruling out secondary insufficiency.[81] Other tests include the insulin hypoglycemia test, the metyrapone test, and the CRH stimulation test.[71]

The standard cutoffs described above are of limited use in acutely ill patients.[71] Severe infection, trauma, burns, illnesses, or surgery can increase cortisol production by as much as a factor of 6, making the recognition of adrenal insufficiency in this population extremely difficult. In the critically ill, a random cortisol concentration below 15 µg/dL (415 nmol/L) is suggestive of adrenal insufficiency, whereas a concentration greater than 34 µg/dL (940 nmol/L) suggests that adrenal insufficiency is unlikely.[71] For patients who fall between these two values, a poor response to corticotropin (<9 µg/dL [250 nmol/L] increase in plasma cortisol from baseline at 30 or 60 minutes) indicates the possibility of adrenal insufficiency and a need for corticosteroid supplementation.[71] A hypoproteinemic patient (albumin <2.5 g/dL [25 g/L]) will have markedly lower CBG, which can underestimate the actual free fraction of cortisol. These patients may benefit from measurement of free cortisol, although the assay may not be routinely available.[71]

TREATMENT

Treatment of Addison disease must include adequate patient education, so that the patient is aware of treatment complications, the expected outcome, consequences of missed doses, and drug side effects. The agents of choice are hydrocortisone and cortisone acetate administered two or three times daily. The treatment goal is to establish the lowest effective dose mimicking the normal diurnal adrenal rhythm.[79] Twice-daily dosing is usually adequate depending on the agent used. Once-daily prednisolone is an alternative when adherence to a multi-dose regimen is a concern.

Endogenous cortisol production varies between 5 and 10 mg/m^2/day.[82] Hence, the classically recommended 12 to 15 mg/m^2/day dose for cortisol supplementation will be excessive in most patients. Starting doses to properly mimic endogenous cortisol production are 15 to 25 mg of hydrocortisone daily, which is roughly equal to 20 to 35 mg of cortisone acetate daily, or 3 to 5 mg of prednisolone daily.[71,82] For hydrocortisone or cortisone, the majority of the dose (67%) is given in the morning and the remainder (33%) is given 6 to 8 hours later to duplicate the normal circadian rhythm of cortisol production. Continuous infusion of glucocorticoids delivered via infusion pump may provide a more physiological circadian maintenance of ACTH and cortisol concentration when compared to conventional oral replacement.[83] Since no laboratory test adequately determines the appropriateness of dosing, the patient's symptoms should be monitored every 6 to 8 weeks to assess proper glucocorticoid replacement. Monitoring parameters should include body weight, postural blood pressures, subjective energy levels, and signs of frank glucocorticoid excess.

In primary insufficiency, fludrocortisone acetate can be used to supplement mineralocorticoid loss. For most patients, a dose of 0.05 to 0.2 mg by mouth once a day is adequate to maintain volume status. If parenteral therapy is needed, 2 to 5 mg of deoxycorticosterone trimethylacetate in oil intramuscularly every 3 to 4 weeks can be substituted. Mineralocorticoid replacement attenuates the development of hyperkalemia, and patients on fludrocortisone therapy do not need to restrict salt intake. However, mineralocorticoid replacement may be unnecessary in some primary cases because glucocorticoids, particularly at large doses, also bind to mineralocorticoid receptors. For example, a daily dose of hydrocortisone 40 to 50 mg has similar mineralocorticoid effects to 0.1 mg of fludrocortisone. Adverse effects must be monitored closely and include gastric upset, edema, hypertension, hypokalemia, insomnia, excitability, and diabetes mellitus. In addition, patient weight, blood pressure, and ECG should be monitored regularly.[71]

Most adrenal crises occur secondary to glucocorticoid dose reduction or lack of stress-related dose adjustments. Patients receiving corticosteroid replacement therapy should receive an additional 5 to 10 mg of hydrocortisone shortly before strenuous activities such as exercise.[71] Likewise, during times of severe physical stress such as febrile illnesses or injury, patients should be instructed to double their daily dose until recovery.[71,84] For major trauma, surgery, or in critically ill patients, larger doses—up to 10 times the usual daily dose—may be required.[71] Parenteral therapy should be used for patients experiencing diarrhea or vomiting. In patients with concomitant, newly diagnosed, or uncontrolled hypothyroidism, thyroid replacement should take place only after adequate glucocorticoid replacement as euthyroidism can trigger an adrenal crisis by accelerating cortisol metabolism.[79]

The endpoint of therapy is difficult to assess in most patients, but a reduction in excess pigmentation is a good clinical marker. The development of features of Cushing syndrome indicates excessive replacement. Treatment of secondary adrenal insufficiency is similar to primary disease treatment, except that mineralocorticoid replacement usually is unnecessary. Patient education is paramount with emphasis placed on the medication regimen and adrenal crisis prevention.

Acute Adrenal Insufficiency

Adrenal crisis, or Addisonian crisis, is characterized by an acute adrenocortical insufficiency and represents a true endocrine emergency. Although no universally accepted definition for adrenal crisis exists, major clinical features include volume depletion and hypotension that resolves within one to two hours after parenteral glucocorticoid administration.[85] Anything that increases adrenal requirements dramatically can precipitate an adrenal crisis. Stressful situations, surgery, infection, and trauma all are potential triggering events, especially in the patient with some underlying adrenal or pituitary insufficiency. The most common cause of an adrenal crisis is HPA-axis suppression brought on by abrupt withdrawal of chronic glucocorticoid use.

Treatment of adrenal crisis involves the administration of parenteral glucocorticoids. Hydrocortisone is the agent of choice owing to its combined glucocorticoid and mineralocorticoid activity. Hydrocortisone is initially administered at a dose of 100 mg IV through rapid infusion, followed by 200 mg of hydrocortisone over 24 hours via a continuous infusion or a 50-mg intermittent bolus every 6 hours.[71] Intravenous administration is continued for an additional day at a reduced dose of 100 mg over 24 hours, at which time if the patient is stable, oral hydrocortisone can be administered at a dose of 50 mg every 6 to 8 hours, followed by tapering to the individual's chronic replacement needs. Fluid replacement often is required and can be accomplished with dextrose 5% in normal saline solution (D_5NS) at a rate to support blood pressure. If therapy is needed for hypoglycemia, dextrose 25% in water ($D_{25}W$) can be infused at a dose of 2 to 4 mL/kg (maximum single dose of 25 g dextrose). During initial treatment for adrenal crisis, mineralocorticoid replacement generally is unnecessary because of hydrocortisone's mineralocorticoid activity. If hyperkalemia is present after the hydrocortisone maintenance phase, additional mineralocorticoid supplementation can be achieved with 0.1 mg of fludrocortisone acetate daily.

Patients with adrenal insufficiency should be instructed to carry a card or wear a bracelet or necklace, such as MedicAlert, that contains information about their condition. Additionally, patients should 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.[71]

Hypoaldosteronism

Hypoaldosteronism is rare and usually associated with low-renin status (hyporeninemic hypoaldosteronism), diabetes, complete heart block, or severe postural hypotension, or it can occur postoperatively following tumor removal. Hypoaldosteronism can be part of a multi-hormonal insufficiency or a stand-alone defect. In nonselective hypoaldosteronism, generalized adrenocortical insufficiency is the most likely etiology (see Addison Disease). In selective hypoaldosteronism, insufficient aldosterone levels are precipitated by a specific defect in the stimulation of adrenal aldosterone secretion, with 21-hydroxylase deficiency being the most common. Pseudohypoaldosteronism results from a defect in peripheral aldosterone action, whether from peripheral resistance or a reduced number of functional aldosterone receptors.

Laboratory analysis reveals hyponatremia, hyperkalemia, or both. Patients often will present with hyperchloremic metabolic acidosis. In most cases, the deficiency is in mineralocorticoid production and fludrocortisone given 0.05 to 0.2 mg daily is usually effective. Patients should be monitored for blood pressure response as well as electrolyte status.

Congenital Adrenal Hyperplasia

Because many enzyme systems are needed to complete the complex cholesterol-to-cortisol pathway, enzyme deficiencies can lead to disruptions of the normal cascade of events (see Fig. 97-2). This group of enzyme disorders is collectively referred to as congenital adrenal hyperplasia (CAH) because of the resultant chronic adrenal gland stimulation that occurs following enzyme deficiency.[71,86,87] The most frequent cause of CAH is steroid 21-hydroxylase deficiency, accounting for more than 90% of cases. Any enzyme deficiency is capable of affecting any one or all three of the steroid pathways. Therefore, treatment focuses on the replacement of the deficient hormone, psychological support, and surgical repair of the external genitalia in female patients.[88] Pediatric patients receiving glucocorticoid replacement (eg, with hydrocortisone and fludrocortisone) should be monitored for adverse outcomes, especially incident hypertension and decreased bone mineral density.[89,90] Six of the most common enzyme deficiencies are outlined briefly in Table 97-12.

TABLE 97-12

Congenital Adrenal Hyperplasia

Enzyme Deficiency (Disorder)	Symptoms	Laboratory Tests	Comments
21-Hydroxylase (nonvirilizing CAH)	Enlarged female genitalia and adrenal gland (caused by cholesterol)	All steroids are low in blood and urine	Poor prognosis for infants
17-Hydroxylase (nonvirilizing CAH)	Hypertension usually present	Low concentrations of cortisol and estrogens	Mineralocorticoid replacement is not necessary
21-Hydroxylase (virilizing CAH)	Pubertal irregularities (acne, early pubic hair, voice lowering, and increased muscularity); mature normally with replacement	High progesterone, renin, 17-hydroxyprogesterone, and ACTH; low cortisol, sodium, and aldosterone	Most common form of CAH (90% of total), incidence of 1:10,000; monitor growth velocity, bone age, renin, and 17-hydroxyprogesterone
11-Hydroxylase (virilizing CAH)	Hypertension secondary to high deoxycortisol and virilism from androgen excess; mistaken for Cushing, but no glucose intolerance	Low plasma cortisone and aldosterone; high ACTH and MSH concentrations	Second most common form of CAH (9% of total), the incidence of 1:100,000; the final step in the biosynthesis of corticosterone and cortisol; found only in the adrenal cortex
3-Hydroxysteroid dehydrogenase (mixed CAH)	Both cortisol and aldosterone deficiencies	Decreased aldosterone, cortisol, estrogens, and androgens; increased pregnenolone and cholesterol	The defect affects both adrenals and gonads
18-Hydroxysteroid dehydrogenase (corticosterone methyloxidase deficiency)	Hypotension	Restricted to zona glomerulosa; sole aldosterone defect; hyponatremia, hyperkalemia, increased renin	Mineralocorticoid replacement without glucocorticoid replacement

CAH, congenital adrenal hyperplasia; ACTH, adrenocorticotropic hormone; MSH, melanocyte-stimulating hormone.

Adrenal Virilism

Virilism, excessive secretion of androgens from the adrenal gland, commonly occurs as a result of congenital enzyme defects. Depending on the enzyme deficiency, patients accumulate excess levels of a variety of androgens, most notably testosterone. The condition affects women more often than men, with hirsutism being the dominant feature. Additional coexisting features can include voice deepening, acne, increased muscle mass, menstrual abnormalities, clitoral enlargement, redistribution of body fat and loss of female body contour, breast atrophy, and hair recession and crown balding.[91]

Treatment of virilism centers on the suppression of the pituitary-adrenal axis with exogenous glucocorticoids. In adults, the usual steroids used are dexamethasone (0.25-0.5 mg), prednisone (2.5-5 mg), or hydrocortisone (10-20 mg).[92]

Hirsutism

Women presenting with hirsutism exhibit excess terminal hair growth in an androgen-dependent distribution. Such growth has obvious cosmetic consequences, but also can adversely affect quality of life and psychological well-being.[93] Most cases of hirsutism occur in women with some degree of excess androgen production. Androgen excess can be derived from either the ovaries or the adrenal glands, or rarely from pituitary disorders. Polycystic ovarian syndrome (PCOS) is responsible for most cases of ovary excess and is the most common cause of hirsutism.[94] CAH accounts for 5% of cases while adrenal and ovarian tumors cause hyperandrogenemia in 0.2% of women.

Cosmetic approaches generally are tried first, with repeated photoepilation offering the greatest long-term success.[95] If these approaches are unsuccessful, subsequent treatment should include pharmacologic intervention. Oral contraceptives are the treatment of choice in most hirsute women, particularly in those requiring concurrent contraception. If oral contraceptives are used, a progestin with low androgen activity (norethindrone, ethynodiol diacetate) or antiandrogenic activity (drospirenone) should be chosen. Other antiandrogens, including spironolactone and finasteride, can supplement or replace oral contraceptive therapy in women who cannot or choose not to conceive. Antiandrogens can take 6 to 12 months to alleviate hirsutism and treatment should be continued for 2 years, followed by a slow dose reduction.[96] Dexamethasone (and other glucocorticoids) can be modestly effective if the androgen source is adrenal, but can induce cushingoid symptoms even at doses of 0.5 mg/day.

Gonadotropin-releasing hormone can be an effective adjunct or alternative to oral contraceptives if the source of androgen is ovarian. However, these products generally are not recommended due to excessive costs, injectable-only routes of administration, and adverse effects resulting from estrogen deficiency. Additionally, insulin sensitizers, such as metformin or thiazolidinediones, can show modest metabolic and glycemic improvement in women with PCOS, but their routine use is not recommended due to their limited impact on hirsutism, acne, and infertility.[94]

Eflornithine hydrochloride, an irreversible ornithine decarboxylase inhibitor, moderately reduces the rate of hair growth but does not remove hair already present. The drug is available as a topical cream applied as a thin layer to the affected area twice daily, at least 8 hours apart. Reduction in unwanted hair can be noted within 6 to 8 weeks with a maximal effect at 8 to 24 weeks; therapy must be continued indefinitely to prevent hair regrowth.[92,96] Skin irritation can occur that resolves on discontinuation.

PRINCIPLES OF GLUCOCORTICOID ADMINISTRATION

The term *glucocorticoid* was initially given to these agents to describe their glucose-regulating properties. However, carbohydrate metabolism is only one of the myriad effects exhibited by steroids. The activity produced by these drugs is a function of the receptor activated (glucocorticoid vs mineralocorticoid), the location of the receptor, as well as the agent and dose prescribed.

The mechanism of action of glucocorticoids is complex and not fully known. The glucocorticoid enters the cell through passive diffusion and binds to its specific receptor. Between 5,000 and 100,000 receptors exist in each cell. Steroids exhibit various binding affinities to the vast number of receptors in almost every tissue and therefore elicit a wide variety of biologic effects.

Following receptor binding, a structural change occurs in the receptor, known as *activation*. After activation, the receptor–steroid complex binds to deoxyribonucleic acid sites in the cell called *glucocorticoid response elements* (GREs). This binding alters nearby gene expression and stimulates or, in some cases, inhibits transcription of specific mRNAs. Consequently, the resulting protein, which produces the stimulatory or inhibitory glucocorticoid action, varies according to the tissue and cell type in which the glucocorticoid receptor exists.

Pharmacokinetic properties of the glucocorticoids vary by agent and route of administration. In general, most orally administered steroids are well absorbed. Water-soluble agents are more rapidly absorbed following intramuscular injection than are lipid-soluble agents. Intravenous administration is recommended when a quick onset of action is needed. A summary of these agents is provided in Table 97-13.

TABLE 97-13

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

In addition to causing iatrogenic Cushing syndrome, systemic steroids can lead to increased susceptibility to infection, osteoporosis, sodium retention with resultant edema, hypokalemia, hypomagnesemia, cataracts, peptic ulcer disease, seizures, and generalized suppression of the HPA axis. Long-term complications tend to be insidious and less likely to respond to steroid withdrawal.

Suppression of the HPA axis is a major concern whenever systemic steroids are tapered or withdrawn. Single doses of glucocorticoids can prevent the axis from responding to major stressors for several hours. In general, steroid administration at a high dose for long periods of time causes suppression of the axis. However, the possibility of suppression occurs any time the patient is exposed to supraphysiologic steroid doses.[11,97] Symptoms of steroid withdrawal resemble those seen in a patient with adrenocortical deficiency.

A variety of recommendations for steroid tapering are available.[11,98-100] In general, patients who have been on long-term steroid therapy will need to be gradually withdrawn toward physiologic doses over months. On average, the normal adult produces approximately 10 to 30 mg of cortisol per day with the peak concentration occurring around 8:00 am. As the steroid or steroid-equivalent dose approaches the 20- to 30-mg level, the taper should be slowed and the patient checked for axis function. The primary modes to test HPA integrity are the ACTH test, either high or low dose, or a morning (8:00 am) serum cortisol. A normal morning serum cortisol (>20 µg/dL [550 nmol/L]) or a normal ACTH test indicates that daily steroid maintenance therapy may be discontinued. If morning serum cortisol is between 3 and 20 µg/dL (85 and 550 nmol/L), the ACTH or CRH stimulation test can be useful in the assessment of pituitary-adrenal function.[11] A morning cortisol less than 3 µg/dL (85 nmol/L) indicates axis suppression and the need for continued replacement therapy. Suppression can persist for up to a year in some patients. Caution should be used to prevent disease exacerbation during the steroid taper and to avoid the need for another course of high-dose steroids.

Alternate-day therapy (ADT) regimens have been promoted as a means to lessen the impact of prolonged steroid administration.[11,100] ADT theoretically minimizes the hypothalamic-pituitary suppression as well as some of the adverse effects seen with once-daily therapy. This hypothetical advantage may be especially pertinent in treating children and young adults, in whom growth suppression is a major concern. ADT is not recommended for initial management, but rather in the management of the stabilized patient who needs long-term therapy. The patient is exposed to "on" and "off" days, with the "on" day dose gradually increased corresponding with a dose reduction in the "off" day dose over a period of 14 days. After 2 weeks, no medication is taken on "off" days. Not all patients will have equivalent disease control on ADT, and it should be avoided in certain indications.[11,100]

EVALUATION OF THERAPEUTIC OUTCOMES

Successful glucocorticoid therapy involves counseling and monitoring the patient, as well as recognizing complications of therapy (Table 97-14). The risk-to-benefit ratio of glucocorticoid administration should always be considered, especially with concurrent disease states such as hypertension, diabetes mellitus, peptic ulcer disease, and uncontrolled systemic infections.

TABLE 97-14

Appropriate Use of Glucocorticoid Therapy

Monitoring	Glucose concentrations (serum and urine) Electrolytes (serum and urine) Ophthalmologic examinations Stool tests for occult blood loss Growth and development (children and adolescents)
Patient education	Take with food to minimize GI discomfort Never discontinue medication on your own; check with your physician; gradual dose reduction is usually necessary Carry or wear medical identification indicating that you are on long-term glucocorticoid therapy Dosage increases can be necessary at times of increased stress (surgery or emergency treatments) Be aware of potential side effects (ie, visual disturbances, bruising, and delayed wound healing) What to do if you miss a dose: If your dosing schedule is: *Every other day*: Take as soon as possible if remembered that morning. If not remembered until later, skip that day. Take the next morning, and then skip the following day *Every day*: Take as soon as possible, but skip if almost time for the next dose. Never double doses
Recognizing complications	Early in therapy and essentially unavoidable: insomnia, enhanced appetite, weight gain Common in patients with underlying risk factors: hypertension, diabetes mellitus, peptic ulcer disease Long-term intense treatment: cushingoid habitus, hypothalamic pituitary-adrenal suppression, impaired wound healing Delayed and insidious: cataracts, atherosclerosis Rare and unpredictable: psychosis, glaucoma, pancreatitis

Data from References 101 and 102.

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
ADT	alternate-day therapy
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APA	aldosterone-producing adenoma
APS	autoimmune polyendocrine syndrome
ARR	aldosterone-to-renin ratio

AST	aspartate aminotransferase
AVS	adrenal venous sampling
BAH	bilateral adrenal hyperplasia
CAH	congenital adrenal hyperplasia
CBG	corticosteroid-binding globulin
CCT	captopril challenge test
CHD	coronary heart disease
CNS	central nervous system
CrCl	creatinine clearance
CRH	corticotropin-releasing hormone
CT	computed tomography
CYP	cytochrome P450
D_5NS	dextrose 5% in normal saline solution
$D_{25}W$	dextrose 25% in water
DDT	dichlorodiphenyltrichloroethane
DST	dexamethasone suppression test
ECG	electrocardiogram
FDA	Food and Drug Administration
FH	familial hyperaldosteronism
FST	fludrocortisone suppression test
GABA	γ-aminobutyric acid
GI	gastrointestinal
GRA	glucocorticoid-remediable aldosteronism
GRE	glucocorticoid response element
HPA	hypothalamic–pituitary–adrenal
INR	international normalized ratio

IPSS	inferior petrosal sinus sampling
IRMA	immunoradiometric assay
JVS	jugular venous sampling
LDL	low-density lipoprotein
MRI	magnetic resonance imaging
PA	primary aldosteronism
PAC	plasma aldosterone concentration
PAC-to-PRA	plasma aldosterone concentration-to-plasma renin activity
PCOS	polycystic ovarian syndrome
POMC	proopiomelanocortin
PRA	plasma renin activity
RAAS	renin-angiotensinaldosterone system
RIA	radioimmunoassay
SIT	saline infusion test
sst	somatostatin receptor subtype
UFC	urinary free cortisolx

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SELF-ASSESSMENT QUESTIONS

1. Aldosterone is synthesized in the:
   A. Zona glomerulosa.
   B. Zona fasciculata.
   C. Zona reticularis.
   D. Medulla.
2. Glucocorticoids regulate their own secretion by inhibiting the pituitary secretion of:
   A. Corticotropin-releasing hormone.
   B. Adrenocorticotropic hormone.
   C. Melanocyte-stimulating hormone.
   D. Renin.
3. The majority of cases of ACTH-dependent Cushing syndrome are caused by
   A. Adrenal carcinoma.
   B. Primary pigmented nodular adrenal disease.
   C. Adrenal adenoma.
   D. Pituitary adenoma.
4. In a 52-year-old male patient with cushingoid habitus, elevated serum and urinary cortisol, very high serum ACTH, no suppression of cortisol in response to low-dose DST, normal pituitary MRI, and no gradient on inferior petrosal sinus sampling (IPSS), the most likely diagnosis would be Cushing syndrome secondary to:
   A. Adrenal carcinoma.
   B. Ectopic ACTH production.
   C. Adrenal adenoma.
   D. Pituitary adenoma.
5. In an adult female patient with classic Cushing disease (caused by an adrenal adenoma), the preferred treatment is:
   A. Mitotane 3 g three times a day.
   B. Pasireotide 0.6 mg twice daily.
   C. Resection of the adrenal tumor.
   D. Mifepristone 300 mg once daily.
6. Which of the following drugs has been associated with an increased risk of serious hepatotoxicity?
   A. Cabergoline

B. Metyrapone

C. Ketoconazole

D. Pasireotide

7. The majority of cases of primary aldosteronism are caused by:

A. Aldosterone-producing adenomas (APA).

B. Bilateral adrenal hyperplasia (BAH).

C. Unilateral adrenal hyperplasia.

D. Familial hyperaldosteronism (FH) type 1.

8. The combination of resistant hypertension, normokalemia, an aldosterone-to-renin ratio (ARR) of 23 ng/dL per ng/(mL·h) (640 pmol/L per mcg/(L·h), plasma aldosterone concentration (PAC) of 19 ng/dL (530 pmol/L), a positive fludrocortisone suppression test, a normal CT, and no lateralization on AVS would be suggestive of:

A. Bilateral adrenal hyperplasia.

B. Aldosterone-producing adenoma.

C. Licorice ingestion.

D. Familial hyperaldosteronism (FH) type 2.

9. The treatment of choice for bilateral adrenal hyperplasia-dependent aldosteronism is:

A. Spironolactone.

B. Mifepristone.

C. Angiotensin receptor blockers.

D. Partial adrenalectomy.

10. Which of the following signs or symptoms is seen in both primary and secondary adrenal insufficiency?

A. Hyperpigmentation

B. Normal aldosterone secretion

C. Normal response to the rapid ACTH stimulation test

D. Weakness

11. The agent of choice for the immediate treatment of acute adrenal insufficiency is:

A. 5% dextrose in normal saline IV.

B. Prednisone 5 mg by mouth.

C. Hydrocortisone 100 mg IV.

D. Fludrocortisone 0.1 mg by mouth.

12. Congenital adrenal hyperplasia (CAH) associated with deficiency in 21-hydroxylase can lead to selective hypoaldosteronism manifesting hyponatremia or hyperkalemia. Which of the following treatment options is preferred for selective hypoaldosteronism?

    A. Mitotane

    B. Spironolactone

    C. Prednisolone

    D. Fludrocortisone

13. Which of the following pharmacologic agents would be first line for treatment of hirsutism in women due to adrenal androgen excess?

    A. Dexamethasone

    B. Ethinyl estradiol and norethindrone

    C. Osilodrostat

    D. Gonadotropin-releasing hormone

14. When tapering long-term steroid therapy, at which of the following steroid doses should the taper be slowed and the HPA axis integrity assessed?

    A. Dexamethasone 6 mg/day

    B. Prednisone 20 mg/day

    C. Cortisone 200 mg/day

    D. Hydrocortisone 40 mg/day

15. Adult patients who will be taking long-term glucocorticoids should be warned about which of the following?

    A. Weight loss and hypersomnia early in therapy

    B. Osteoporosis and glaucoma with chronic therapy

    C. Growth suppression

    D. Need for reduced glucocorticoid dosing during times of increased stress

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** The zona glomerulosa preferentially produces aldosterone owing to a lack of 17-hydroxylase activity, greater aldosterone synthase activity, and greater angiotensin II receptor expression than other adrenal cortex zones.

2. **B.** In response to a decrease in circulating glucocorticoid concentrations, the median eminence of the hypothalamus releases corticotropin-releasing hormone which stimulates adrenocorticotropic hormone from the pituitary gland. As glucocorticoid concentrations increase, a negative feedback loop decreases the release of corticotropin-releasing hormone from the hypothalamus and adrenocorticotropic hormone from the pituitary gland.

3. **D.** Approximately 85% of ACTH-dependent Cushing syndromes are caused by pituitary adenomas.

4. **B.** Abnormal cortisol concentrations, no suppression of cortisol from low-dose DST, elevated concentrations of ACTH, normal pituitary MRI, and no gradient on IPSS favor an ectopic production etiology. See Fig. 97-4.

5. **C.** Surgical resection of offending tumors is the treatment of choice for Cushing disease. Generally pharmacotherapy is reserved as second-line

therapy in patients awaiting surgery or as adjunctive to surgery as the pharmacologic agents are associated with limited efficacy and significant side effects.

6. **C.** Ketoconazole has been associated with serious hepatotoxicity, leading regulatory authorities to restrict ketoconazole use in certain types of fungal infections (in the United States) or to remove oral ketoconazole from the market altogether (in Europe).

7. **B.** Bilateral adrenal hyperplasia causes approximately 65% of primary aldosteronism cases. The next most common etiology, aldosterone-producing adenomas, causes approximately 30% of primary aldosteronism cases.

8. **A.** Hypertension with hypo or normokalemia, ARR ≥20 ng/dL per ng/(mL·h) (550 pmol/L per mcg/(L·h)), PAC ≥15 ng/dL (420 pmol/L), unsuppressed aldosterone with a fludrocortisone suppression test, normal CT, and no lateralization on AVS would indicate bilateral adrenal hyperplasia type primary aldosteronism. For diagnosis, FH type 2 would require genetic testing and licorice ingestion would require a relevant diet history and a low PAC.

9. **A.** An aldosterone receptor antagonist is the treatment of choice for bilateral adrenal hyperplasia. Spironolactone, a nonselective aldosterone receptor antagonist, competes with aldosterone for binding at aldosterone receptors which prevent downstream effects of aldosterone receptor activity.

10. **D.** Primary adrenal insufficiency generally presents with excess ACTH causing hyperpigmentation and is associated with an abnormal response to ACTH due to decreased aldosterone secretion. Conversely, secondary adrenal insufficiency is characterized by normal aldosterone secretion and a normal response to the ACTH test, but with decreased baseline ACTH that presents can present with hypopigmentation. Both are associated with weakness.

11. **C.** Hydrocortisone is used as initial therapy for adrenal crisis as it has combined glucocorticoid and mineralocorticoid activity. If hyperkalemia persists during hydrocortisone maintenance of adrenal insufficiency, additional mineralocorticoid supplementation can be added utilizing fludrocortisone.

12. **D.** 21-hydroxylase deficiency reduces synthesis of glucocorticoids and mineralocorticoids. Selective hypoaldosteronism is associated with insufficient aldosterone levels due to a defect in stimulation of adrenal aldosterone secretion. Therefore, appropriate medical management includes exogenous mineralocorticoids (eg, fludrocortisone).

13. **B.** Oral contraceptives (eg, ethinyl estradiol and norethindrone) are the treatment of choice in most women with hirsutism. Dexamethasone and gonadotropin-releasing hormone are alternatives to oral contraceptives but are associated with increased side effects and limited efficacy.

14. **D.** A steroid taper should be slowed, and HPA axis integrity assessed, when the steroid dose approaches the equivalent of 20 to 30 mg of cortisol. Of the options, only hydrocortisone (cortisol) 40 mg/day is near this average amount, whereas the other glucocorticoid doses are much greater than physiologic doses of cortisol and it can be assumed that these doses are suppressing the HPA axis.

15. **B.** Osteoporosis and glaucoma are associated with long-term glucocorticoid therapy, especially when used at supraphysiologic doses. Weight gain and insomnia can also occur. Growth suppression is a concern in pediatric patients, but not typically adults. Generally, patients who have decreased ability to produce glucocorticoids will not be able to increase glucocorticoid production in response to increased stress. Therefore, patients with increased stress should be administered an increased dose of glucocorticoid rather than a decreased dose.