on a negative result. Assuming a 25–30% ROM for nodules with indeterminate cytology, the negative predictive values for the currently validated molecular tests are >95%.

The evaluation of a thyroid nodule is stressful for most patients. They are concerned about the possibility of thyroid cancer, whether verbalized or not. It is constructive, therefore, to review the diagnostic approach and to reassure patients when no malignancy is found. When a suspicious lesion or thyroid cancer is identified, the generally favorable prognosis and available treatment options can be reassuring.

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398 Disorders of the Adrenal Cortex

Wiebke Arlt, Alessandro Prete

The adrenal cortex produces three classes of corticosteroid hormones: glucocorticoids (e.g., cortisol), mineralocorticoids (e.g., aldosterone), and adrenal androgen precursors (e.g., dehydroepiandrosterone [DHEA]) **(Fig. 398-1)**. Glucocorticoids and mineralocorticoids act through specific nuclear receptors, regulating aspects of the physiologic stress response as well as blood pressure and electrolyte homeostasis. Adrenal androgen precursors are converted in the gonads and peripheral target cells to sex steroids that act via nuclear androgen and estrogen receptors.

Disorders of the adrenal cortex are characterized by deficiency or excess of one or several of the three major corticosteroid classes. Hormone deficiency can be caused by inherited glandular or enzymatic disorders or by destruction of the pituitary or adrenal gland by autoimmune disorders, infection, infarction, or iatrogenic events such as surgery or hormonal suppression. Hormone excess is usually the result of neoplasia, leading to increased production of adrenocorticotropic hormone (ACTH) by the pituitary or neuroendocrine ectopic ACTH-producing cells or increased production of glucocorticoids, mineralocorticoids, or adrenal androgen precursors by adrenal nodules or hyperplasia. Adrenal nodules are increasingly identified incidentally during cross-sectional imaging of the chest or abdomen performed for other reasons.

ADRENAL ANATOMY AND DEVELOPMENT

The normal adrenal glands weigh 6–11 g each. They are located above the kidneys and have their own blood supply. Arterial blood flows initially to the subcapsular region and then meanders from the outer cortical zona glomerulosa through the intermediate zona fasciculata to the inner zona reticularis and eventually to the adrenal medulla. The right adrenal (or suprarenal) vein drains directly into the vena cava, while the left adrenal vein drains into the left renal vein.

During early embryonic development, the adrenals originate from the urogenital ridge and then separate from gonads and kidneys at about the sixth week of gestation. Concordant with the time of sexual differentiation (seventh to ninth week of gestation, **Chap. 402**), the adrenal cortex starts to produce cortisol and the adrenal sex steroid precursor DHEA. The orphan nuclear receptors SF1 (steroidogenic factor 1; encoded by the gene *NR5A1*) and DAX1 (dosage-sensitive sex reversal gene 1; encoded by the gene *NR0B1*), among others, play a crucial role during this period of development, as they regulate a multitude of adrenal genes involved in steroidogenesis.

REGULATORY CONTROL OF STEROIDOGENESIS

Production of glucocorticoids and adrenal androgens is under the control of the hypothalamic-pituitary-adrenal (HPA) axis, whereas mineralocorticoids are regulated by the renin-angiotensin-aldosterone (RAA) system.

Glucocorticoid synthesis is under inhibitory feedback control by the hypothalamus and the pituitary **(Fig. 398-2)**. Hypothalamic release of corticotropin-releasing hormone (CRH) occurs in response to endogenous or exogenous stress. CRH stimulates the cleavage of the 241–amino acid polypeptide proopiomelanocortin (POMC) by pituitary-specific prohormone convertase 1 (PC1), yielding the 39–amino acid peptide ACTH. ACTH is released by the corticotrope cells of the anterior pituitary and acts as the pivotal regulator of adrenal cortisol synthesis, with additional short-term effects on mineralocorticoid and adrenal androgen synthesis. The release of CRH, and subsequently ACTH, occurs in a pulsatile fashion that follows a circadian rhythm under the control of the hypothalamus, specifically its suprachiasmatic nucleus (SCN), with additional regulation by a complex network of cell-specific clock genes. The circadian release of ACTH is mostly regulated by the CRH, but arginine-vasopressin (AVP) also exerts a secretagogue role. Reflecting the pattern of ACTH secretion, adrenal cortisol secretion exhibits a distinct circadian rhythm, starting to rise in the early morning hours prior to awakening, with peak levels in the morning and low levels in the evening **(Fig. 398-3)**.

Diagnostic tests assessing the HPA axis make use of the fact that it is regulated by negative feedback. Glucocorticoid excess is diagnosed by employing a dexamethasone suppression test. Dexamethasone, a potent synthetic glucocorticoid, suppresses CRH/ACTH by binding hypothalamic-pituitary glucocorticoid receptors (GRs) and, therefore, results in downregulation of endogenous cortisol synthesis. Various versions of the dexamethasone suppression test are described in detail in **Chap. 392**. If cortisol production is autonomous (e.g., adrenal nodule), ACTH is already suppressed, and dexamethasone has little additional effect. If cortisol production is driven by an ACTH-producing pituitary adenoma, dexamethasone suppression is ineffective at lower doses but usually induces suppression at higher doses. If cortisol production is driven by an ectopic source of ACTH, the tumors are usually resistant to dexamethasone suppression. Thus, the dexamethasone suppression test is useful to establish the diagnosis of Cushing's syndrome and assist with the differential diagnosis of cortisol excess.

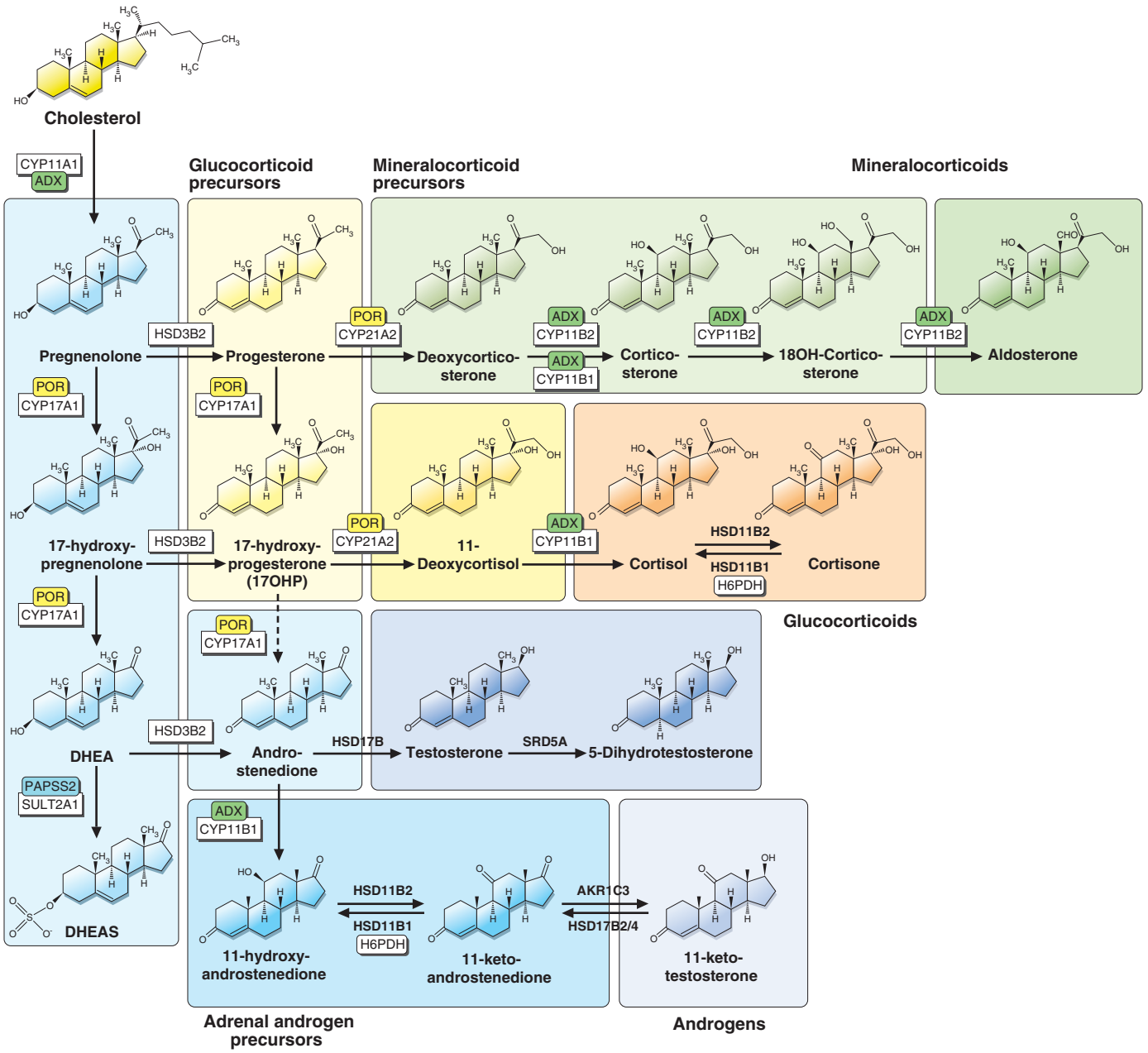

FIGURE 398-1 Adrenal steroidogenesis. ADX, adrenodoxin; AKR1C3, aldo-keto reductase 1C3; CYP11A1, side chain cleavage enzyme; CYP11B1, 11β-hydroxylase; CYP11B2, aldosterone synthase; CYP17A1, 17α-hydroxylase/17,20 lyase; CYP21A2, 21-hydroxylase; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; H6PDH, hexose-6-phosphate dehydrogenase; HSD11B1, 11β-hydroxysteroid dehydrogenase type 1; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; HSD17B, 17β-hydroxysteroid dehydrogenase; HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; PAPSS2, PAPS synthase type 2; POR, P450 oxidoreductase; SRD5A, 5α-reductase; SULT2A1, DHEA sulfotransferase.

Conversely, to assess glucocorticoid deficiency, ACTH stimulation of cortisol production is used. The ACTH peptide contains 39 amino acids, but the first 24 are sufficient to elicit a physiologic response. The standard ACTH stimulation test involves the administration of cosyntropin (ACTH 1-24), 250 μg IM or IV, and collection of blood samples at 0, 30, and optionally 60 min for cortisol. A normal response is defined as a cortisol level >15–20 μg/dL (>400–550 nmol/L) 30–60 min after cosyntropin stimulation, with the precise cutoff dependent on the assay used. A low-dose (1 μg cosyntropin IV) version of this test has been advocated; however, it has no superior diagnostic value and is more cumbersome to carry out due to the lack of commercially available preparations of 1 μg cosyntropin. Alternatively, an insulin tolerance test (ITT) can be used to assess adrenal function. It involves injection of insulin to induce hypoglycemia, which represents a strong stress signal that triggers hypothalamic CRH release and activation of the entire HPA axis. The ITT involves administration of regular insulin 0.1 U/kg IV (dose should be lower if hypopituitarism is likely) and collection of blood samples at 0, 30, 60, and 120 min for glucose, cortisol, and growth hormone (GH), if also assessing the GH axis. Oral or IV glucose is administered after the patient has achieved symptomatic hypoglycemia (usually plasma glucose <40 mg/dL). A normal response is defined as a cortisol >20 μg/dL and GH >5.1 μg/L, again with assay-specific cutoff variability. The ITT requires careful clinical monitoring and sequential measurements of glucose. It is contraindicated in patients with coronary disease, cerebrovascular disease, or seizure disorders, which has made the cosyntropin test the commonly accepted first-line test. The overnight metyrapone test is alternatively used in some centers: metyrapone—a drug blocking the conversion of 11-deoxycortisol to cortisol by 11β-hydroxylase (see treatment of Cushing's syndrome)—is administered orally at midnight (2500 mg or 30 mg/kg). In healthy individuals, the decrease in cortisol stimulates CRH and ACTH production, resulting in an increase in 11-deoxycortisol. A normal response consists of an early morning serum 11-deoxycortisol concentration >287 nmol/L (10 μg/dL). The use of home-waking salivary cortisone as a measure of adrenal cortisol reserve looks highly promising and represents a potential alternative noninvasive test that can be undertaken at home.

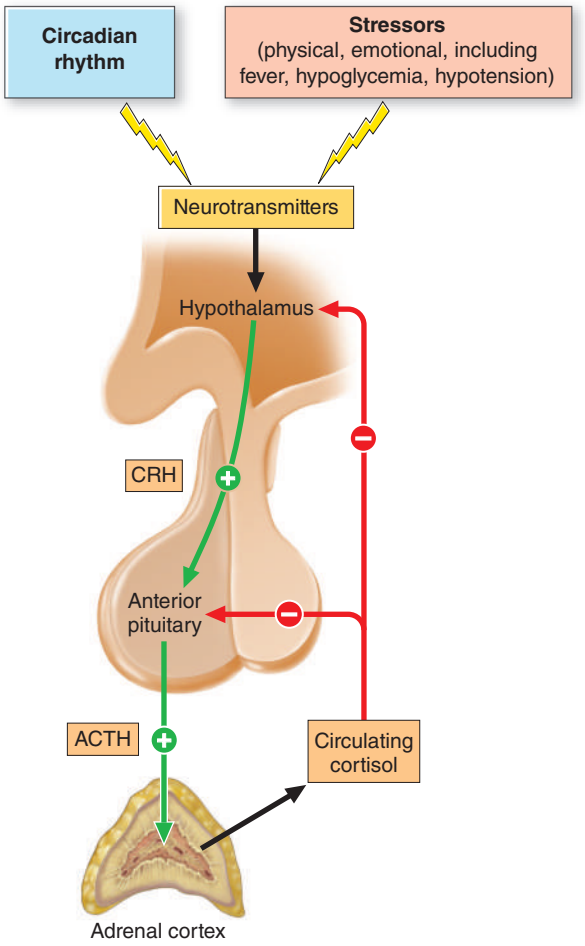

FIGURE 398-2 Regulation of the hypothalamic-pituitary-adrenal (HPA) axis. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

Mineralocorticoid production is controlled by the RAA regulatory cycle, which is initiated by the release of the enzyme renin from the juxtaglomerular cells in the kidney, resulting in cleavage of hepatic angiotensinogen to angiotensin I (Fig. 398-4). The angiotensin-converting enzyme (ACE) cleaves angiotensin I to angiotensin II, which binds and activates the angiotensin II receptor type 1 (AT1 receptor [AT1R]), resulting in increased adrenal aldosterone production and vasoconstriction. Aldosterone enhances renal sodium retention and potassium excretion resulting in volume expansion and increased renal perfusion, which in turn regulates renin release. Because mineralocorticoid synthesis is primarily under the control of the RAA system, hypothalamic-pituitary damage does not significantly impact the capacity of the adrenal to synthesize aldosterone.

Similar to the HPA axis, the assessment of the RAA system can be used for diagnostic purposes. If mineralocorticoid excess is present, there is a counterregulatory downregulation of plasma renin (see below for testing). Conversely, in mineralocorticoid deficiency, plasma renin is markedly increased. Physiologically, oral or IV sodium loading results in suppression of aldosterone, a response that is attenuated or absent in patients with autonomous mineralocorticoid excess.

STEROID HORMONE BIOSYNTHESIS, METABOLISM, AND ACTION

ACTH stimulation is required for the initiation of steroidogenesis. The ACTH receptor MC2R (melanocortin 2 receptor) interacts with the MC2R-accessory protein MRAP, and the complex is transported to the adrenocortical cell membrane, where it binds to ACTH (Fig. 398-5). ACTH stimulation generates cyclic AMP (cAMP), which upregulates the protein kinase A (PKA) signaling pathway. Inactive PKA is a tetramer of two regulatory and two catalytic subunits that is dissociated by cAMP into a dimer of two regulatory subunits bound to cAMP and two free and active catalytic subunits. PKA activation impacts steroidogenesis in three distinct ways: (1) increases the import of cholesterol esters; (2) increases the activity of hormone-sensitive lipase, which cleaves cholesterol esters to cholesterol for import into the mitochondrion; and (3) increases the availability and phosphorylation of CREB (cAMP response element binding), a transcription factor that enhances transcription of CYP11A1 and other enzymes required for glucocorticoid synthesis.

Adrenal steroidogenesis occurs in a zone-specific fashion, with mineralocorticoid synthesis occurring in the outer zona glomerulosa, glucocorticoid synthesis in the zona fasciculata, and adrenal androgen biosynthesis in the inner zona reticularis serving as precursors for both classic and 11-oxygenated androgens (Fig. 398-1). All steroidogenic pathways require cholesterol import into the mitochondrion, a process initiated by the action of the steroidogenic acute regulatory (StAR) protein, which shuttles cholesterol from the outer to the inner mitochondrial membrane. The majority of steroidogenic enzymes are cytochrome P450 (CYP) enzymes, which are either located in the mitochondrion (side chain cleavage enzyme, CYP11A1; 11β-hydroxylase, CYP11B1; aldosterone synthase, CYP11B2) or in the endoplasmic reticulum membrane (17α-hydroxylase, CYP17A1; 21-hydroxylase, CYP21A2; aromatase, CYP19A1). These enzymes require electron donation via specific redox cofactor enzymes, P450 oxidoreductase (POR), and adrenodoxin/adrenodoxin reductase (ADX/ADR) for the microsomal and mitochondrial CYP enzymes, respectively. In addition, the short-chain dehydrogenase 3β-hydroxysteroid dehydrogenase type 2 (3β-HSD2), also termed Δ4, Δ5 isomerase, plays a major role in adrenal steroidogenesis.

The cholesterol side chain cleavage enzyme CYP11A1 generates pregnenolone. Glucocorticoid synthesis requires conversion of pregnenolone to progesterone by 3β-HSD2, followed by conversion to 17-hydroxyprogesterone (17OHP) by CYP17A1, further hydroxylation at carbon 21 by CYP21A2, and eventually, 11β-hydroxylation by CYP11B1 to generate active cortisol (Fig. 398-1). Mineralocorticoid synthesis also requires progesterone, which is first converted to deoxycorticosterone (DOC) by CYP21A2 and then converted via corticosterone and 18-hydroxycorticosterone to aldosterone in three steps catalyzed by CYP11B2. For adrenal androgen synthesis, pregnenolone undergoes conversion by CYP17A1, which uniquely catalyzes two enzymatic reactions. Via its 17α-hydroxylase activity, CYP17A1

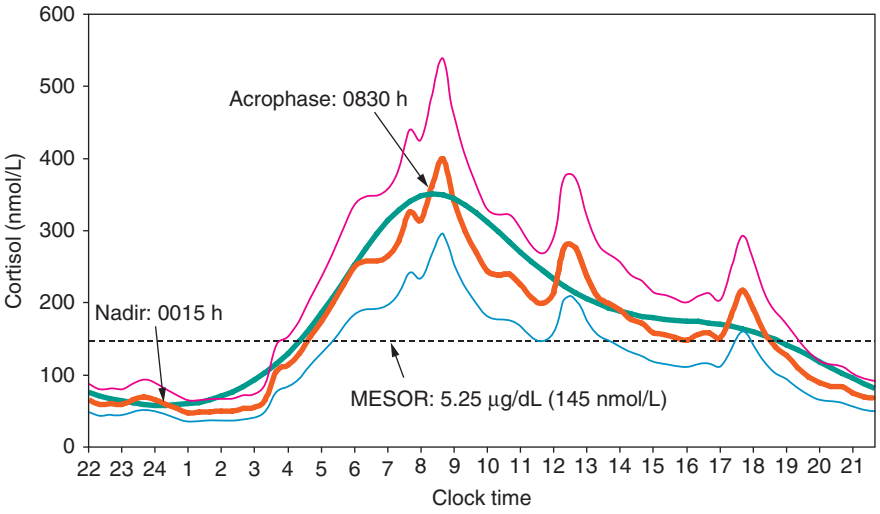

FIGURE 398-3 Physiologic cortisol circadian rhythm. Circulating cortisol concentrations (geometrical mean ± standard deviation values and fitted cosinor) drop under the rhythm-adjusted mean (MESOR) in the early evening hours, with nadir levels around midnight and a rise in the early morning hours; peak levels are observed ~8:30 A.M. (acrophase). *(Reproduced with permission from M Debono et al: Modified-release hydrocortisone to provide circadian cortisol profiles. J Clin Endocrinol Metab 94:1548, 2009.)*

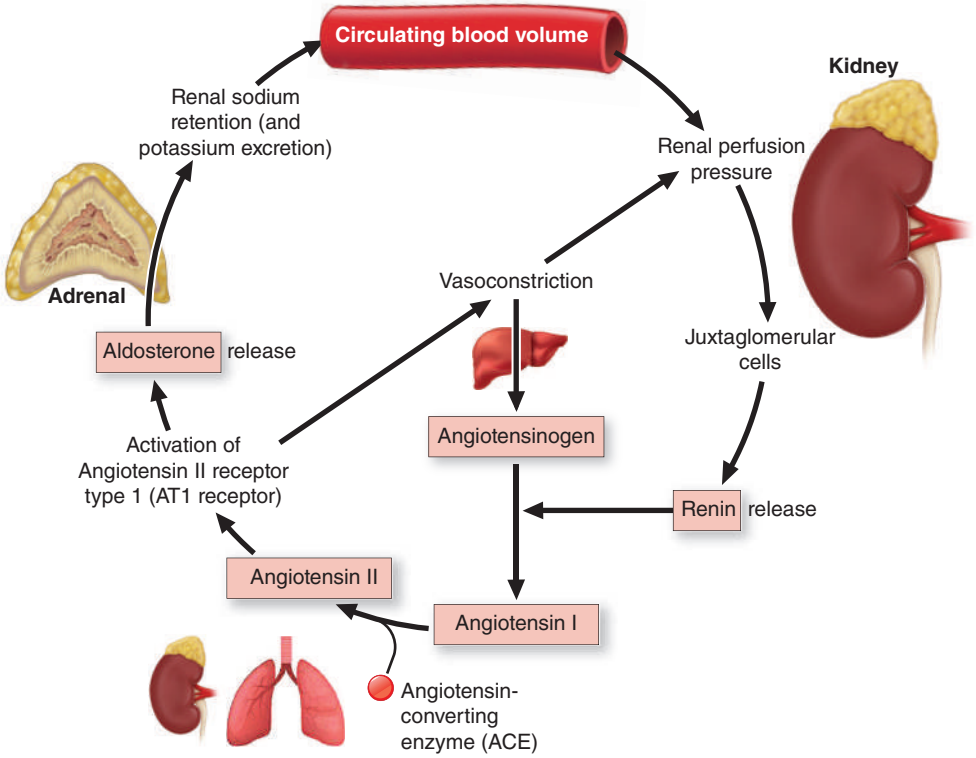

FIGURE 398-4 Regulation of the renin-angiotensin-aldosterone (RAA) system.

converts pregnenolone to 17-hydroxypregnenolone, followed by generation of the universal sex steroid precursor DHEA via CYP17A1 17,20 lyase activity. The majority of DHEA is secreted by the adrenal in the form of its sulfate ester, DHEAS, generated by DHEA sulfotransferase (SULT2A1). DHEA is converted to androstenedione, which can be activated to testosterone or channeled into the 11-oxygenated androgen pathway by 11β-hydroxylation (CYP11B1).

Following its release from the adrenal, cortisol circulates in the bloodstream mainly bound to cortisol-binding globulin (CBG) and, to a lesser extent, to albumin, with only a minor fraction circulating as free, unbound hormone. Free cortisol is thought to enter cells directly, not requiring active transport. In addition, in a multitude of peripheral target tissues of glucocorticoid action, including adipose, liver, muscle, and brain, cortisol is generated from inactive cortisone within the cell by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) (Fig. 398-6). Thereby, 11β-HSD1 functions as a tissue-specific prereceptor regulator of glucocorticoid action. For the conversion of inactive cortisone to active cortisol, 11β-HSD1 requires nicotinamide adenine

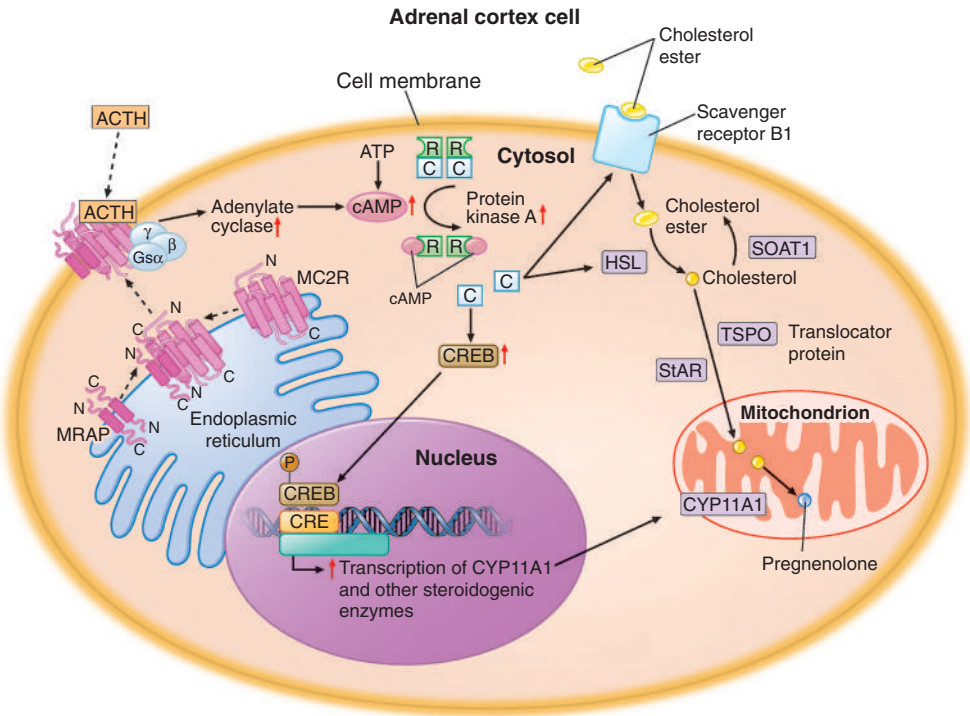

FIGURE 398-5 ACTH effects on adrenal steroidogenesis. ACTH, adrenocorticotropic hormone; CREB, cAMP response element–binding protein; HSL, hormone-sensitive lipase; MRAP, MC2R-accessory protein; protein kinase A catalytic subunit (C; *PRKACA*), PKA regulatory subunit (R; *PRKAR1A*); SOAT1, sterol O-acyltransferase 1; StAR, steroidogenic acute regulatory (protein); TSPO, translocator protein.

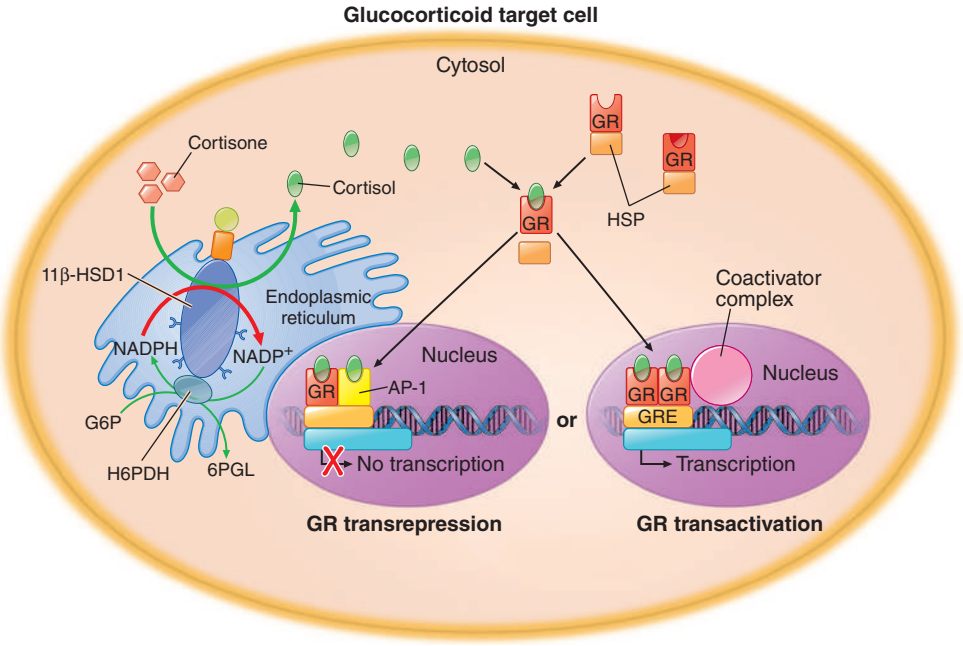

FIGURE 398-6 Prereceptor activation of cortisol and glucocorticoid receptor (GR) action. AP-1, activator protein-1; G6P, glucose-6-phosphate; GREs, glucocorticoid response elements; HSPs, heat shock proteins; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); 6PGL, 6-phosphogluconate.

dinucleotide phosphate (NADPH [reduced form]), which is provided by the enzyme hexose-6-phosphate dehydrogenase (H6PDH). Like the catalytic domain of 11β-HSD1, H6PDH is located in the lumen of the endoplasmic reticulum and converts glucose-6-phosphate (G6P) to 6-phosphogluconate (6PGL), thereby regenerating $NADP^+$ to NADPH, which drives the activation of cortisol from cortisone by 11β-HSD1.

In the cytosol of target cells, cortisol binds and activates the GR, which results in dissociation of heat shock proteins (HSPs) from the receptor and subsequent dimerization (Fig. 398-6). Cortisol-bound GR dimers translocate to the nucleus and activate glucocorticoid response elements (GREs) in the DNA sequence, thereby enhancing transcription of glucocorticoid-regulated genes (GR transactivation). However, cortisol-bound GR can also form heterodimers with transcription factors such as AP-1 or nuclear factor-κB (NF-κB), resulting in transrepression of proinflammatory genes, a mechanism of major importance for the anti-inflammatory action of glucocorticoids. It is important to note that corticosterone also exerts glucocorticoid activity, albeit much weaker than cortisol itself. However, in rodents, corticosterone is the major glucocorticoid, and in patients with 17-hydroxylase deficiency, lack of cortisol can be compensated for by higher concentrations of corticosterone that accumulates as a consequence of the enzymatic block.

Cortisol is inactivated to cortisone by the microsomal enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) **(Fig. 398-7)**, mainly in the kidney, but also in the colon, salivary glands, and other mineralocorticoid target tissues. Cortisol and aldosterone bind the mineralocorticoid receptor (MR) with equal affinity; however, cortisol circulates in the bloodstream at about a 1000-fold higher concentration. Thus, only rapid inactivation of cortisol to cortisone by 11β-HSD2 prevents MR activation by excess cortisol, thereby acting as a tissue-specific modulator of the MR pathway. In addition to cortisol and aldosterone, DOC (Fig. 398-1) also exerts mineralocorticoid activity. DOC accumulation due to 11β-hydroxylase deficiency or due to tumor-related excess production can result in mineralocorticoid excess.

Aldosterone synthesis in the adrenal zona glomerulosa cells is driven by the enzyme aldosterone synthase (CYP11B2). The binding of angiotensin II to the AT1 receptor causes glomerulosa cell membrane depolarization by increasing intracellular sodium through inhibition of sodium-potassium (Na^+/K^+) ATPase enzymes as well as potassium channels. This drives an increase in intracellular calcium by opening voltage-dependent calcium channels or inhibition of calcium (Ca^{2+}) ATPase enzymes. Consequently, the calcium signaling pathway is triggered, resulting in upregulation of CYP11B2 transcription **(Fig. 398-8)**.

Analogous to cortisol action via the GR, aldosterone (or cortisol) binding to the MR in the kidney tubule cell dissociates the HSP-receptor complex, allowing homodimerization of the MR and translocation of the hormone-bound MR dimer to the nucleus (Fig. 398-7). The activated MR enhances transcription of the epithelial sodium channel (ENaC) and serum glucocorticoid-inducible kinase 1 (SGK-1). In the cytosol, interaction of ENaC with Nedd4 prevents cell surface expression of ENaC. However, SGK-1 phosphorylates serine residues within the Nedd4 protein, reduces the interaction between Nedd4 and ENaC, and consequently, enhances the trafficking of ENaC to the cell surface, where it mediates sodium retention at the expense of potassium extrusion through the renal outer medullary potassium channel (ROMK) channel.

CUSHING'S SYNDROME

(See also Chap. 392) Cushing's syndrome reflects a constellation of clinical features that result from chronic exposure to excess glucocorticoids of any etiology. The disorder can be ACTH-dependent (e.g., pituitary corticotrope adenoma, ectopic secretion of ACTH by nonpituitary tumor) or ACTH-independent (e.g., adrenocortical adenoma, adrenocortical carcinoma [ACC], nodular adrenal hyperplasia), as well as iatrogenic (e.g., administration of exogenous glucocorticoids to treat various inflammatory conditions). The term *Cushing's disease* refers specifically to Cushing's syndrome caused by a pituitary corticotrope adenoma.

Epidemiology Iatrogenic (or exogenous) Cushing's syndrome is by far the most common etiology, considering that around 1% of the population uses chronic glucocorticoid treatments for their anti-inflammatory and immunosuppressive properties. On the contrary, endogenous Cushing's syndrome is generally considered a rare disease; it occurs with an incidence of 1.8–3.2 per million population per year. However, it is debated whether mild cortisol excess may be more prevalent among patients with features of Cushing's such as centripetal obesity, type 2 diabetes, and osteoporotic vertebral fractures, recognizing that these are relatively nonspecific and common in the population.

Etiology In the overwhelming majority of patients with endogenous Cushing's syndrome, the underlying cause is an ACTH-producing pituitary neuroendocrine tumor, i.e., a corticotrope adenoma **(Table 398-1)**, as initially described by Harvey Cushing in 1912. Cushing's disease more frequently affects women, with the exception of prepubertal cases, where it is more common in boys. By contrast, ectopic

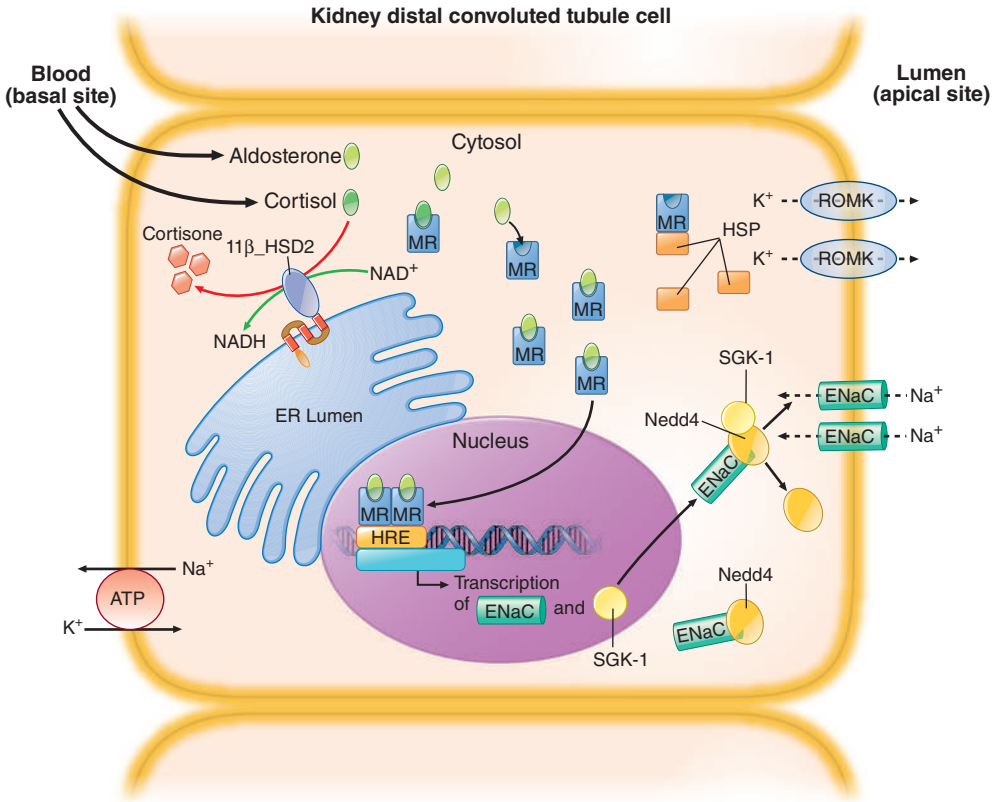

FIGURE 398-7 Prereceptor inactivation of cortisol and mineralocorticoid receptor action. ENaC, epithelial sodium channel; HRE, hormone response element; Na^+/K^+-ATPase, sodium-potassium adenosine triphosphatase; NADH, nicotinamide adenine dinucleotide; ROMK, renal outer medullary potassium channel; SGK-1, serum glucocorticoid-inducible kinase-1.

ACTH syndrome is more frequently identified in men. Only 10% of patients with Cushing's syndrome have a primary, adrenal cause of their disease (i.e., autonomous cortisol excess independent of ACTH), and most of these patients are women.

In at least 90% of patients with Cushing's disease, ACTH excess is caused by a corticotrope pituitary microadenoma, often only a few millimeters in diameter. Pituitary macroadenomas (i.e., tumors >1 cm in size) are found in only 5–10% of patients and may have invasive features and affect the optic chiasm and the cavernous sinuses. Pituitary corticotrope adenomas usually occur sporadically but very rarely can be found in the context of multiple endocrine neoplasia type 1 (MEN 1) **(Chap. 400)**, MEN 4, familial isolated pituitary adenomas, Carney complex, DICER 1 syndrome, and Lynch syndrome. Pituitary adenomas causative of Cushing's disease frequently harbor activating somatic variants in the *USP8* gene, encoding the deubiquitinating enzyme ubiquitin-specific protease 8, which lead to constitutive activation of epidermal growth factor (EGF) signaling and consequent upregulated expression of the ACTH precursor POMC. *USP8* mutations are found in 11–62% of corticotrope adenomas and more frequently in adults and women with Cushing's disease. Less frequently, somatic variants of the glucocorticoid receptor gene (*NR3C1*), *BRAF*, *USP48*, and *TP53* are observed in the tumor tissue of *USP8* wild-type Cushing's disease cases.

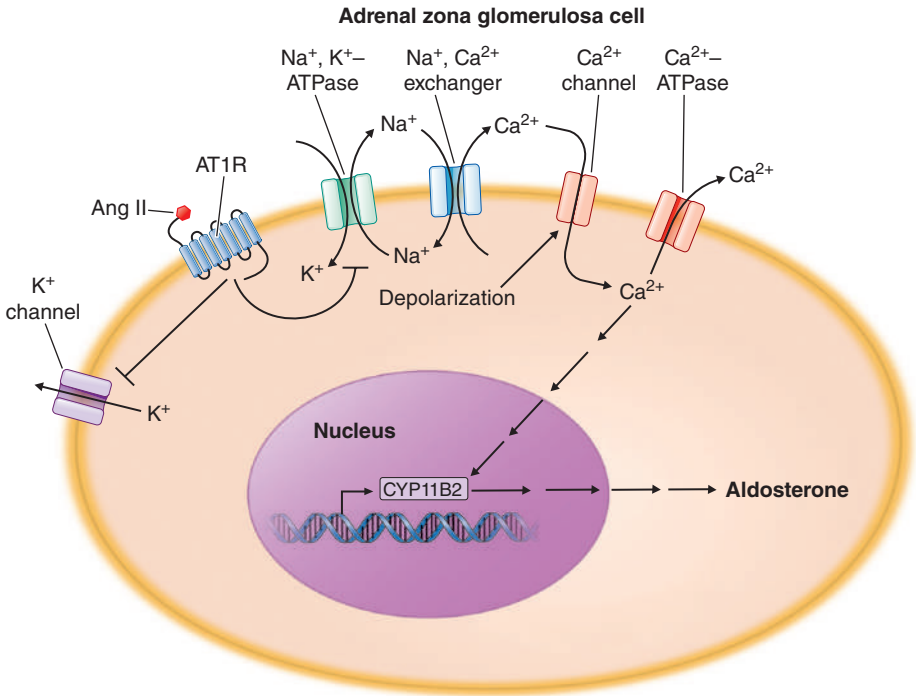

FIGURE 398-8 Regulation of adrenal aldosterone synthesis. Ang II, angiotensin II; AT1R, angiotensin II receptor type 1; CYP11B2, aldosterone synthase.

Ectopic ACTH production is predominantly caused by occult carcinoid tumors, most frequently in the lung, but also in the thymus or pancreas. Because of their small size, these tumors are often difficult to locate. Advanced small-cell lung cancer can cause ectopic ACTH production. In rare cases, ectopic CRH and/or ACTH production has been found to originate from medullary thyroid carcinoma or pheochromocytoma, the latter co-secreting catecholamines and ACTH.

The majority of patients with endogenous ACTH-independent cortisol excess harbor a cortisol-producing adrenal adenoma, and

TABLE 398-1 Causes of Endogenous Cushing's Syndrome

	FEMALE:MALE RATIO	%
ACTH-Dependent Cushing's Syndrome		**90**
Cushing's disease (= ACTH-producing pituitary adenoma)	4:1	75
Ectopic ACTH syndrome (due to ACTH secretion by bronchial or pancreatic carcinoid tumors, small-cell lung cancer, medullary thyroid carcinoma, pheochromocytoma, and others)	1:1	15
ACTH-Independent Cushing's Syndrome	**4:1**	**10**
Adrenocortical adenoma		5–10
Adrenocortical carcinoma		1
Rare causes: macronodular adrenal hyperplasia; primary pigmented nodular adrenal disease (micro- and/or macronodular); McCune-Albright syndrome		<1

Abbreviation: ACTH, adrenocorticotropic hormone.

activating somatic mutations in the PKA catalytic subunit *PRKACA* have been identified as the cause of disease in 40% of these tumors. Somatic inactivating defects of *PRKAR1A*, encoding one of the regulatory subunits of PKA, and *GNAS*, encoding the stimulatory G protein alpha subunit 1 GNAS-1 (guanine nucleotide-binding protein alpha stimulating activity polypeptide 1), have been observed less frequently in unilateral cortisol-producing adenomas. ACCs may also cause ACTH-independent cortisol excess and are often large, with excess production of several corticosteroid classes.

A rare but notable cause of adrenal cortisol excess is primary bilateral macronodular adrenal hyperplasia (PBMAH) with low circulating ACTH but with evidence for autocrine stimulation of cortisol production via intra-adrenal ACTH production. These hyperplastic nodules are often also characterized by aberrant expression of G protein–coupled receptors not usually found in the adrenal, including receptors for luteinizing hormone, vasopressin, serotonin, interleukin 1, catecholamines, or gastric inhibitory peptide (GIP), the cause of food-dependent Cushing's. Activation of these receptors results in upregulation of PKA signaling, as physiologically occurs with ACTH, with a subsequent increase in cortisol production. A combination of germline and somatic mutations in the tumor-suppressor gene *ARMC5* have been identified as a prevalent cause of Cushing's due to bilateral macronodular adrenal hyperplasia; these patients often present with biochemical evidence of Cushing's but lack specific clinical signs, which develop slowly over decades and accelerate cardiovascular risk. Constitutively activating *PRKACA* mutations and inactivating *KDM1A* variants (lysine-specific histone demethylase 1A) can also be a rare cause of bilateral macronodular adrenal hyperplasia, the latter associated with GIP-dependent Cushing's syndrome. Bilateral macronodular adrenal hyperplasia with cortisol excess has also been described in other familial syndromes: MEN 1, hereditary leiomyomatosis and renal cell cancer (*FH* gene), and familial adenomatous polyposis (*APC* gene).

Germline mutations in *PRKAR1A* are found in patients with primary pigmented nodular adrenal disease (PPNAD) as part of *Carney's complex*, an autosomal dominant multiple neoplasia condition associated with cardiac and cutaneous myxomas, hyperlentiginosis, Sertoli cell tumors, ovarian tumors, breast tumors, thyroid nodules, Schwannomas, and PPNAD. PPNAD can present as micronodular or macronodular hyperplasia, or both. Phosphodiesterases can influence intracellular cAMP and can thereby impact PKA activation. Mutations in *PDE11A* and *PDE8B* have been identified in patients with bilateral adrenal hyperplasia and Cushing's, with and without evidence of PPNAD.

Another rare cause of ACTH-independent Cushing's is *McCune-Albright syndrome*, also associated with polyostotic fibrous dysplasia, unilateral café-au-lait spots, and precocious puberty. McCune-Albright syndrome is caused by *GNAS* activating mutations (Table 398-1; **Chap. 424**).

TABLE 398-2 Signs and Symptoms of Cushing's Syndrome

BODY COMPARTMENT/ SYSTEM	SIGNS AND SYMPTOMS
Body fat	Weight gain, central obesity, rounded face, fat pad on back of neck ("buffalo hump")
Skin	Facial plethora, thin and brittle skin, easy bruising, broad and purple stretch marks, acne, hirsutism
Bone	Osteopenia, osteoporosis (vertebral fractures), decreased linear growth in children
Muscle	Weakness, proximal myopathy (prominent atrophy of gluteal and upper leg muscles with difficulty climbing stairs or getting up from a chair)
Cardiovascular system	Hypertension, hypokalemia, edema, atherosclerosis
Metabolism	Glucose intolerance/diabetes, dyslipidemia
Reproductive system	Decreased libido; in women, amenorrhea (due to cortisol-mediated inhibition of gonadotropin release)
Central nervous system	Irritability, emotional lability, depression, insomnia and disrupted sleep, sometimes cognitive defects; in severe cases, paranoid psychosis
Blood and immune system	Increased susceptibility to infections, increased white blood cell count, eosinopenia, hypercoagulation with increased risk of deep vein thrombosis and pulmonary embolism

Clinical Manifestations Glucocorticoids affect almost all cells of the body; thus, signs of cortisol excess impact multiple physiologic systems **(Table 398-2)**, with upregulation of gluconeogenesis, lipolysis, and protein catabolism causing the most prominent features. In addition, excess glucocorticoid secretion overcomes the ability of 11β-HSD2 to rapidly inactivate cortisol to cortisone in the kidney, thereby exerting mineralocorticoid actions, manifest as hypertension, hypokalemia, and edema. Excess glucocorticoids also interfere with central regulatory systems, leading to suppression of gonadotropins with subsequent hypogonadism and amenorrhea and suppression of the hypothalamic-pituitary-thyroid axis, resulting in decreased thyroid-stimulating hormone (TSH) secretion.

The majority of clinical signs and symptoms observed in Cushing's syndrome are relatively nonspecific and include features such as obesity, diabetes, diastolic hypertension, hirsutism, and depression that are commonly found in patients who do not have Cushing's. Therefore, careful clinical assessment is an important aspect of evaluating suspected cases. A diagnosis of Cushing's should be considered when several clinical features are found in the same patient, particularly when more specific features are found or manifest at an unusual age, e.g., osteoporosis in a young patient. Distinct features include thinning and fragility of the skin, with easy bruising and broad (>1 cm), purplish striae **(Fig. 398-9)**, and signs of proximal myopathy, which becomes most obvious when trying to stand up from a chair without the use of hands or when climbing stairs. Clinical manifestations of Cushing's do not differ substantially among the different causes of Cushing's. In ectopic ACTH syndrome, hyperpigmentation of the knuckles, scars, or skin areas exposed to increased friction can be observed (Fig. 398-9) and is caused by stimulatory effects of excess ACTH and other POMC cleavage products on melanocyte pigment production. Furthermore, patients with ectopic ACTH syndrome, and some with ACC as the cause of Cushing's, may have a more rapid onset and progression of clinical signs and symptoms, namely edema, hypokalemia, and hypertension.

Patients with Cushing's syndrome can be acutely endangered by deep vein thrombosis, with subsequent pulmonary embolism, due to a hypercoagulable state associated with cortisol excess. The majority of patients also experience psychiatric symptoms, mostly in the form of anxiety or depression, but acute paranoid or depressive psychosis may occur. Even after cure, long-term health may be affected by persistently impaired health-related quality of life and increased risk of cardiovascular disease and osteoporosis with vertebral fractures, depending on the duration and degree of exposure to significant cortisol excess.

FIGURE 398-9 Clinical features of Cushing's syndrome. ***A.*** Note central obesity and broad, purple stretch marks (***B.*** close-up). ***C.*** Note thin and brittle skin in an elderly patient with Cushing's syndrome. ***D.*** Hyperpigmentation of the knuckles in a patient with ectopic adrenocorticotropic hormone (ACTH) excess.

Diagnosis The most important first step in the management of patients with suspected Cushing's syndrome is to establish the correct diagnosis. Most mistakes in clinical management, leading to unnecessary imaging or surgery, are made because the diagnostic protocol is not followed **(Fig. 398-10)**. This protocol requires establishing the diagnosis of Cushing's beyond doubt prior to employing any tests used for the differential diagnosis of the condition. In principle, after excluding exogenous glucocorticoid use as the cause of clinical signs and symptoms, suspected cases should be tested if there are multiple and progressive features of Cushing's, particularly features with a potentially higher discriminatory value. Exclusion of cortisol excess is also indicated in patients with incidentally discovered adrenal masses.

A diagnosis of Cushing's can be considered as established if the results of several tests are consistently suggestive of Cushing's. These tests may include increased 24-h urinary free cortisol excretion in three separate collections, failure to appropriately suppress morning serum cortisol after overnight exposure to dexamethasone, and evidence of loss of diurnal cortisol secretion with high levels of serum or salivary cortisol at midnight, the time of the physiologically lowest secretion (Fig. 398-10). Factors potentially affecting the outcome of these diagnostic tests have to be excluded such as incomplete 24-h urine collection or rapid inactivation of dexamethasone due to concurrent intake of CYP3A4-inducing drugs (e.g., antiepileptics, rifampicin). Concurrent intake of oral contraceptives that raise CBG and thus total cortisol can cause failure to suppress after dexamethasone. If in doubt, testing should be repeated after 4–6 weeks off oral estrogens. Patients with pseudo-Cushing states, e.g., alcohol-related nonneoplastic hypercortisolism or associated with major depression or morbid obesity, as well as those with cyclic Cushing's syndrome, may require further testing to safely confirm or exclude the diagnosis of Cushing's. In addition, the biochemical assays employed can affect the test results, with specificity representing a common problem with antibody-based assays for the measurement of urinary free cortisol. These assays have been greatly improved by the introduction of highly specific tandem mass spectrometry.

Differential Diagnosis The evaluation of patients with confirmed Cushing's should be carried out by an endocrinologist and begins with the differential diagnosis of ACTH-dependent and ACTH-independent cortisol excess (Fig. 398-10). Generally, plasma ACTH levels are suppressed in cases of autonomous adrenal cortisol excess, consequent to enhanced negative feedback to the hypothalamus and pituitary. By contrast, patients with ACTH-dependent Cushing's have normal or increased plasma ACTH, with very high levels being found in some patients with ectopic ACTH syndrome. Importantly, imaging should only be used after it is established whether the cortisol excess is ACTH-dependent or ACTH-independent because nodules in the pituitary or the adrenal are a common finding in the general population. In patients with confirmed ACTH-independent excess, adrenal imaging is indicated **(Fig. 398-11)**, preferably using an unenhanced computed tomography (CT) scan. This allows assessment of adrenal morphology and also the determination of tumor density, i.e., the attenuation value measured in Hounsfield units (HUs), which helps to distinguish between benign and malignant adrenal lesions (note, this only applies to unenhanced CT; postcontrast CT does not convey this information).

For ACTH-dependent cortisol excess **(Chap. 392)**, a magnetic resonance image (MRI) of the pituitary is the investigation of choice, but it may not show an abnormality in up to 40% of cases because of small tumors below the sensitivity of detection. Characteristically, pituitary corticotrope adenomas fail to enhance following gadolinium administration on T1-weighted MRI images. In all cases of confirmed ACTH-dependent Cushing's, further tests are required for the differential diagnosis of pituitary Cushing's disease and ectopic ACTH syndrome. These tests exploit the fact that most pituitary corticotrope adenomas still display regulatory features, including residual ACTH suppression by high-dose glucocorticoids and responsiveness to CRH or desmopressin, a synthetic analog of vasopressin. In contrast, ectopic sources of ACTH are typically resistant to dexamethasone suppression and unresponsive to CRH or desmopressin (Fig. 398-10). However, it should be noted that a small minority of ectopic ACTH-producing

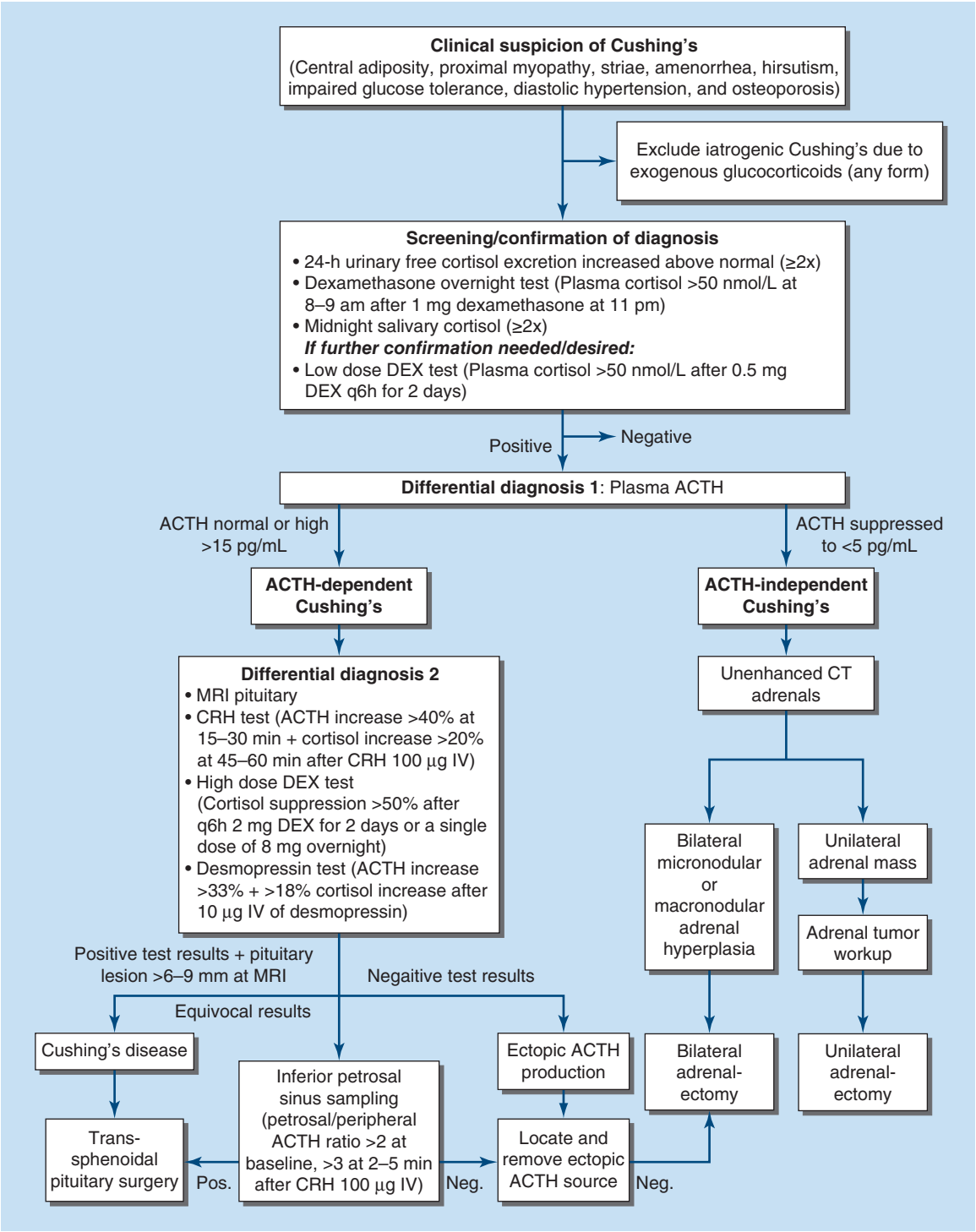

FIGURE 398-10 Management of the patient with suspected Cushing's syndrome. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CT, computed tomography; DEX, dexamethasone; MRI, magnetic resonance imaging.

tumors exhibit dynamic responses similar to pituitary corticotrope tumors. If the tests show discordant results or if there is any other reason for doubt, the differential diagnosis can be further clarified by performing bilateral inferior petrosal sinus sampling (IPSS) with concurrent blood sampling for ACTH in the right and left inferior petrosal sinus and a peripheral vein. An increased central/peripheral plasma ACTH ratio >2 at baseline and >3 at 2–5 min after CRH injection is indicative of Cushing's disease (Fig. 398-10), with very high sensitivity and specificity. Of note, the results of the IPSS cannot be reliably used for lateralization (i.e., prediction of the location of the tumor within the pituitary) because there is broad interindividual variability in the venous drainage of the pituitary region. Importantly, no cortisol-lowering agents should be used prior to IPSS.

If the differential diagnostic testing indicates ectopic ACTH syndrome, then further imaging should include high-resolution, fine-cut CT scanning of the chest and abdomen for scrutiny of the lung, thymus, and pancreas. If no lesions are identified, an MRI of the chest can be considered because carcinoid tumors usually show high signal intensity on T2-weighted images. Furthermore, octreotide scintigraphy and ^{68}Ga DOTATATE positron emission tomography (PET)/CT can be helpful in some cases because ectopic ACTH-producing tumors often express somatostatin receptors. Depending on the suspected cause, patients with ectopic ACTH syndrome should also undergo blood sampling for fasting gut hormones, chromogranin A, calcitonin, and biochemical exclusion of pheochromocytoma.

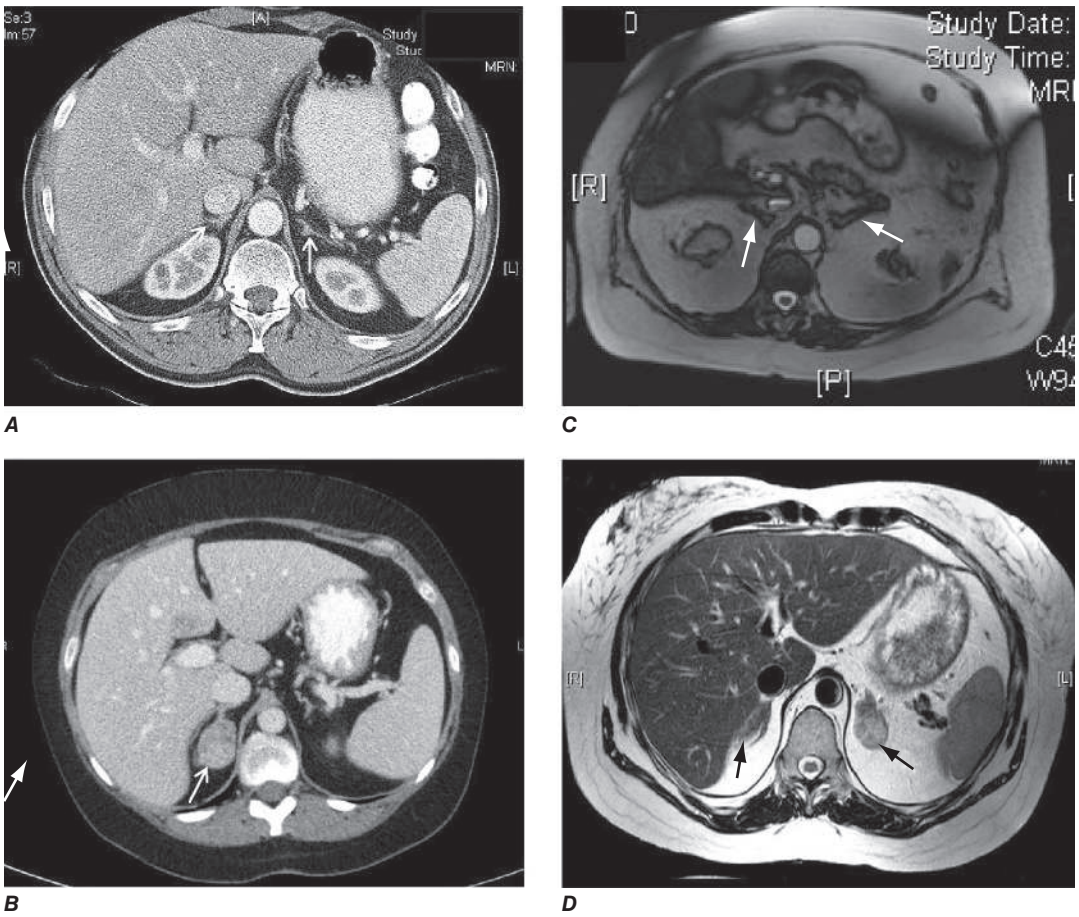

FIGURE 398-11 Adrenal imaging in Cushing's syndrome. ***A.*** Adrenal computed tomography (CT) showing normal bilateral adrenal morphology (*arrows*). ***B.*** CT scan depicting a right adrenocortical adenoma (*arrow*) causing Cushing's syndrome. ***C.*** Magnetic resonance imaging (MRI) showing bilateral adrenal hyperplasia due to excess adrenocorticotropic hormone stimulation in Cushing's disease. ***D.*** MRI showing bilateral macronodular hyperplasia causing Cushing's syndrome.

TREATMENT

Cushing's Syndrome

Overt Cushing's is associated with a poor prognosis if left untreated. In ACTH-independent disease, treatment consists of surgical removal of the adrenal tumor or nodular hyperplasia. For benign tumors, a minimally invasive laparoscopic approach can be used, whereas for those suspected of malignancy, an open approach is preferred.

In Cushing's disease, the treatment of choice is selective removal of the pituitary corticotrope tumor, usually via an endoscopic transsphenoidal approach. This results in an initial cure rate of 60–80% when performed by a highly experienced surgeon, although remission rates are much lower (12–70%) in patients presenting with larger or invasive tumors. Even after initial remission following surgery, long-term follow-up is important because late relapse occurs in a significant number of patients. If pituitary disease persists after surgery or recurs after initial remission, there are several options including second surgery, fractionated radiotherapy, stereotactic radiosurgery, pharmacologic therapy, and bilateral adrenalectomy. These options need to be applied in a highly individualized fashion.

In some patients with very severe, overt Cushing's (e.g., difficult-to-control hypokalemic hypertension, acute psychosis, or life-threatening infections), it may be necessary to introduce medical therapy to rapidly control the cortisol excess during the period leading up to surgery, which also can help to alleviate hypercoagulability and, thus, operative risk. Similarly, patients with metastasized, glucocorticoid-producing carcinomas may require long-term antiglucocorticoid drug treatment. In the case of ectopic ACTH syndrome, in which the tumor cannot be located, one must carefully weigh whether drug treatment or bilateral adrenalectomy is the most appropriate choice, with the latter facilitating immediate cure but requiring life-long corticosteroid replacement. In this instance, it is paramount to ensure regular imaging follow-up for identification of the ectopic ACTH source.

Oral agents with established efficacy in Cushing's syndrome are osilodrostat, metyrapone, ketoconazole, levoketoconazole, and mifepristone. Osilodrostat and metyrapone inhibit cortisol synthesis at the level of 11β-hydroxylase (Fig. 398-1). The antimycotic drug ketoconazole, and its stereoisomer levoketoconazole, inhibit the early steps of steroidogenesis. Mifepristone is a GR blocker, hence mitigating the effects of cortisol excess on target tissues. Typical starting doses are 1–2 mg bid for osilodrostat (maximum daily dose, 60 mg), 500 mg tid for metyrapone (maximum daily dose, 6 g), 200 mg tid for ketoconazole (maximum daily dose, 1200 mg), 150 mg bid for levoketoconazole (maximum daily dose, 1200 mg), and 300 mg for mifepristone (maximum daily dose, 1200 mg). Mitotane, a derivative of the insecticide o,p'DDD, is an adrenolytic agent that is also effective for reducing cortisol. Because of its side effect profile, it is most commonly used in the context of ACC, but low-dose treatment (500–1000 mg/d) has also been used in benign Cushing's. In severe cases of cortisol excess, etomidate, an agent that potently blocks 11β-hydroxylase and aldosterone synthase, can be used to rapidly lower cortisol. It is administered by continuous IV infusion in low, nonanesthetic doses. For Cushing's disease, the subcutaneous or intramuscular administration of pasireotide, a somatostatin receptor agonist, represents another therapeutic option, if surgical cure cannot be achieved. The dopamine agonist cabergoline is also used off-label to treat certain patients with Cushing's disease, especially those with mild cortisol excess and/or residual tumor due to the potential for tumor shrinkage.

After the successful removal of an ACTH- or cortisol-producing tumor, the HPA axis will remain suppressed. Thus, hydrocortisone replacement needs to be initiated at the time of surgery and slowly tapered following recovery, to allow physiologic adaptation to normal cortisol levels. Depending on the degree and duration of cortisol excess, the HPA axis may require many months or even years to resume normal function and sometimes does not recover. Generally, ectopic ACTH syndrome shows the best recovery rate (80%; median time to recovery 7 months) and adrenal Cushing's has the lowest (40%; median time to recovery 30 months), with Cushing's disease intermediate (60%; median time to recovery 17 months).

PRIMARY MINERALOCORTICOID EXCESS

Epidemiology Following the first description of a patient with an aldosterone-producing adrenal adenoma (*Conn's syndrome*), mineralocorticoid excess was thought to represent a rare cause of hypertension. However, in studies systematically screening all patients with hypertension, a much higher prevalence is now recognized, ranging from 5 to 12%. The prevalence is higher when patients are preselected for hypokalemic hypertension or drug-resistant hypertension.

Etiology The most common cause of primary (i.e., adrenal) mineralocorticoid excess is primary aldosteronism, reflecting excess production of aldosterone by the adrenal zona glomerulosa. Traditionally, the main subtypes of the disease are bilateral primary aldosteronism due to bilateral micronodular adrenal hyperplasia (the most common form) and unilateral aldosterone-producing adenoma (Conn's syndrome) (Table 398-3). Although recent evidence has shown that primary aldosteronism exists on a spectrum blurring the line between bilateral and unilateral forms, their binary distinction underpins clinical management because unilateral forms are amenable to potentially curative surgery, whereas mineralocorticoid receptor antagonist therapy is the treatment of choice for bilateral forms. Somatic mutations in channels and enzymes responsible for increasing sodium and calcium influx in adrenal zona glomerulosa cells have been identified as prevalent causes of aldosterone-producing adrenal adenomas (Table 398-3) and, in the case of germline mutations, also of familial forms of primary aldosteronism. Sporadic bilateral adrenal hyperplasia as a cause of mineralocorticoid excess is usually micronodular but can also contain larger nodules that might be mistaken for a unilateral adenoma. Genetic forms of primary aldosteronism, which account for up to 6% of cases, should be suspected in patients with severe hypertension diagnosed

TABLE 398-3 Causes of Primary Mineralocorticoid Excess

CAUSES OF PRIMARY MINERALOCORTICOID EXCESS	MECHANISM	%
Sporadic Primary Aldosteronism		**94–99**
Adrenal (Conn's) adenoma	Autonomous aldosterone excess can be caused by somatic (intratumor) mutations in the potassium channel GIRK4 (encoded by *KCNJ5*; identified as cause of disease in 40–70% of aldosterone-producing adenomas and associated with overproduction of hybrid steroids). Further causes include somatic mutations affecting the α-subunit of the Na^+/K^+-ATPase (encoded by *ATP1A1*), the plasma membrane calcium-transporting ATPase 3 (encoded by *ATP2B3*), the voltage-gated calcium channel CaV1.3 and CaV3.2 (encoded by *CACNA1D* and *CACNA1H*, respectively), and the ClC-2 chloride channel (encoded by *CLCN2*). All mutations result in the upregulation of CYP11B2 and hence aldosterone synthesis. Rarely, somatic mutations affecting β-catenin (encoded by *CTNNB1*) have been observed alone or in combination with *CACNA1D* mutations and are presumed to promote an increase in the number of aldosterone-producing cells.	30–40
Bilateral adrenal hyperplasia	Bilateral autonomous aldosterone excess due to aldosterone-producing diffuse hyperplasia and/or multiple aldosterone-producing micronodules. *CACNA1D* somatic mutations have been described in 58% of aldosterone-producing micronodules of patients with bilateral aldosterone excess who underwent unilateral adrenalectomy as a nonstandard treatment.	60–70
Familial Primary Aldosteronism		**1–6**
Type 1 (also known as glucocorticoid-remediable hyperaldosteronism or dexamethasone-suppressible hyperaldosteronism)	Autosomal dominant. Crossover between the *CYP11B1* and *CYP11B2* genes results in ACTH-driven aldosterone production. Characterized by severe hypertension in childhood or young adults (often <20 years), with a high risk of cardiovascular events including hemorrhagic stroke at a young age due to ruptured intracranial aneurysm. Analysis of adrenal steroidogenesis shows overproduction of hybrid steroids.	
Type 2	Autosomal dominant. The most common form (1–6% of adults with primary aldosteronism). Due to germline *CLCN2* mutations. Variable phenotypic presentation, which typically includes early-onset hypertension.	
Type 3	Autosomal dominant. Germline *KCNJ5* mutations. Characterized by severe early-onset hypertension (<20 years) with massive bilateral macronodular adrenal hyperplasia. Analysis of adrenal steroidogenesis shows overproduction of hybrid steroids.	
Type 4	Autosomal dominant. Germline *CACNA1H* mutations. Characterized by severe early-onset hypertension (<20 years), which can be associated with developmental disorders in some cases.	
Primary aldosteronism, seizures, and neurologic abnormalities (PASNA)	De novo *CACNA1D* mutations. Characterized by childhood-onset hypertension, seizures, neurologic abnormalities, congenital hyperinsulinism, and cardiac abnormalities.	
Other Causes (Rare)		**<1**
Syndrome of apparent mineralocorticoid excess (SAME)	Mutations in *HSD11B2* result in lack of renal inactivation of cortisol to cortisone, leading to excess activation of the MR by cortisol (inhibition of 11β-hydroxysteroid dehydrogenase type 2 by excess licorice ingestion can have similar effects).	
Cushing's syndrome	Cortisol excess overcomes the capacity of HSD11B2 to inactivate cortisol to cortisone, consequently flooding the MR.	
Glucocorticoid resistance	Upregulation of cortisol production due to GR mutations results in flooding of the MR by cortisol.	
Adrenocortical carcinoma	Autonomous aldosterone and/or DOC excess.	
Congenital adrenal hyperplasia	Accumulation of DOC due to mutations in *CYP11B1* or *CYP17A1*.	
Progesterone-induced hypertension	Progesterone acts as an abnormal ligand due to mutations in the MR gene.	
Liddle's syndrome	Mutant ENaC β or γ subunits resulting in reduced degradation of ENaC keeping the membrane channel in open conformation for longer, enhancing mineralocorticoid action.	

Abbreviations: ACTH, adrenocorticotropic hormone; DOC, deoxycorticosterone; ENaC, epithelial sodium channel; GR, glucocorticoid receptor; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; MR, mineralocorticoid receptor.

during childhood or young adulthood (Table 398-3). In rare instances, primary aldosteronism is caused by an ACC. Carcinomas should be considered in younger patients and in those with larger tumors because benign aldosterone-producing adenomas usually measure <2 cm in diameter.

A rare cause of aldosterone excess is glucocorticoid-remediable aldosteronism (GRA), or type 1 familial primary aldosteronism, which is caused by a chimeric gene resulting from the crossover of promoter sequences between the *CYP11B1* and *CYP11B2* genes that are involved in glucocorticoid and mineralocorticoid synthesis, respectively (Fig. 398-1). This rearrangement brings *CYP11B2* transcription under the control of ACTH receptor signaling; consequently, aldosterone production is regulated by ACTH rather than by renin. The family history can be helpful because there may be evidence for dominant transmission of hypertension. Recognition of the disorder is important because it can be associated with early-onset hypertension and strokes. In addition, glucocorticoid suppression can reduce aldosterone production. The adrenal glands of patients with GRA produce high levels of the hybrid steroids 18-oxocortisol and 18-hydroxycortisol due to the coexistence of CYP11B1 and CYP11B2 enzymatic activities in the same steroidogenic cells, which are normally segregated to the zona fasciculata and glomerulosa, respectively. Similarly, high hybrid steroid levels are observed in patients with aldosterone-producing adenomas harboring somatic *KCNJ5* mutations (encoding the potassium channel GIRK4) and type 3 familial primary aldosteronism due to germline *KCNJ5* mutations (Table 398-3). Hybrid steroids are produced by normal adrenal glands in very low concentrations and can therefore be measured in the blood and urine to identify these conditions.

Other rare causes of primary mineralocorticoid excess are listed in Table 398-3. An important cause is excess binding and activation of the MR by a steroid other than aldosterone. Cortisol acts as a potent mineralocorticoid if it escapes efficient inactivation to cortisone by 11β-HSD2 in the kidney (Fig. 398-7). This can be caused by inactivating mutations in the *HSD11B2* gene resulting in the syndrome of apparent mineralocorticoid excess (SAME) that characteristically manifests with severe hypokalemic hypertension in childhood. However, milder mutations may cause normokalemic hypertension manifesting in adulthood (type II SAME). Inhibition of 11β-HSD2 by excess licorice ingestion also results in hypokalemic hypertension, as does overwhelming of 11β-HSD2 conversion capacity by cortisol excess in Cushing's syndrome. DOC also binds and activates the MR and can cause hypertension if its circulating concentrations are increased. This can arise through autonomous DOC secretion by an ACC, but also when DOC accumulates as a consequence of an adrenal enzymatic block, as seen in congenital adrenal hyperplasia (CAH) due to CYP11B1 (11β-hydroxylase) or CYP17A1 (17α-hydroxylase) deficiency (Fig. 398-1). Progesterone can cause hypokalemic hypertension in rare individuals who harbor a MR mutation that enhances binding and activation by progesterone; physiologically, progesterone normally exerts antimineralocorticoid activity. Finally, excess mineralocorticoid activity can be caused by mutations in the β or γ subunits of the ENaC, disrupting its interaction with Nedd4 (Fig. 398-7), and thereby decreasing receptor internalization and degradation. The constitutively active ENaC drives hypokalemic hypertension, resulting in an autosomal dominant disorder termed *Liddle's syndrome*.

Clinical Manifestations Excess activation of the MR leads to potassium depletion and increased sodium retention, with the latter causing an expansion of extracellular and plasma volume. Increased ENaC activity also results in hydrogen depletion, which can cause metabolic alkalosis. Aldosterone also has direct effects on the vascular system, where it increases cardiac remodeling and decreases compliance. Aldosterone excess may cause direct damage to the myocardium and the kidney glomeruli, in addition to secondary damage due to systemic hypertension.

The clinical hallmark of mineralocorticoid excess is hypokalemic hypertension; however, only 10–40% of patients with primary aldosteronism exhibit hypokalemia. Serum sodium tends to be normal due to the concurrent fluid retention, which in some cases can lead to peripheral edema. Hypomagnesemia is also a common finding. Hypokalemia can be exacerbated by thiazide drug treatment, which leads to increased delivery of sodium to the distal renal tubule, thereby driving potassium excretion. Severe hypokalemia can be associated with polyuria, glucose intolerance, muscle weakness, overt proximal myopathy, or even arrhythmias, rhabdomyolysis, and hypokalemic paralysis. Severe alkalosis contributes to muscle cramps and, in severe cases, can cause tetany.

Of note, patients with primary aldosteronism show increased rates of osteoporosis, type 2 diabetes, and cognitive dysfunction. A significant proportion of patients with primary aldosteronism suffer from concurrent mild autonomous cortisol secretion (MACS), a constellation also termed *Connshing syndrome*.

Diagnosis Diagnostic screening for mineralocorticoid excess is not currently recommended for all patients with hypertension but should be restricted to those who exhibit hypertension associated with drug resistance, hypokalemia, an adrenal mass, onset of disease before the age of 40 years, or family history of primary aldosteronism **(Fig. 398-12)**. The accepted screening test is concurrent measurement of plasma renin and aldosterone with subsequent calculation of the aldosterone-renin ratio (ARR) (Fig. 398-12); serum potassium needs to be normalized prior to testing. Stopping antihypertensive medication can be cumbersome, particularly in patients with severe hypertension. Thus, for practical purposes, in the first instance, the patient can remain on the usual antihypertensive medications, with the exception that MR antagonists need to be ceased at least 4–6 weeks prior to ARR measurement. The remaining antihypertensive drugs may also affect the outcome of ARR testing (e.g., beta-blocker treatment can cause false-positive results and ACE/AT1R inhibitors can cause false-negative results in milder cases and may have to be discontinued for 2–4 weeks in case of repeat testing) **(Table 398-4)**. The decision to arrange washout from potentially interfering medications should be individualized.

Current international guidelines suggest a positive ARR screening result is >750 pmol/L per ng/mL per hour, with a concurrently high normal or increased aldosterone (Fig. 398-12). However, lower ARR cutoffs are routinely used in clinical practice since it is increasingly recognized that milder forms of primary aldosteronism may otherwise be missed. Another consideration is that if one relies on the ARR only, the likelihood of a false-positive ARR becomes greater when renin levels are very low. The characteristics of the biochemical assays are also important. Some labs measure plasma renin activity, whereas others measure plasma renin concentrations. Antibody-based assays for the measurement of serum aldosterone lack the reliability of tandem mass spectrometry assays, but these are not yet ubiquitously available.

Diagnostic confirmation of mineralocorticoid excess in a patient with a positive ARR screening result should be undertaken by an endocrinologist as the tests lack optimized validation. The most straightforward is the saline infusion test, which involves the IV administration of 2 L of physiologic saline over a 4-h period. Failure of aldosterone to suppress <170 pmol/L (6 ng/dL) in the seated position or <140 pmol/L (5 ng/dL) in the recumbent position is indicative of autonomous mineralocorticoid excess. Alternative tests are the oral sodium loading test (300 mmol NaCl/d for 3 days) or the fludrocortisone suppression test (0.1 mg q6h with 30 mmol NaCl q8h for 4 days); the latter can be difficult because of the risk of profound hypokalemia and increased hypertension. In patients with overt hypokalemic hypertension, strongly positive ARR, and concurrently increased aldosterone levels, confirmatory testing is usually not necessary.

Differential Diagnosis and Treatment After the diagnosis of hyperaldosteronism is established, the next step is to use adrenal imaging to further assess the cause. Fine-cut CT scanning of the adrenal region is the method of choice because it provides excellent visualization of adrenal morphology, and most aldosterone-producing adenomas are <2 cm. CT will readily identify larger tumors suspicious of malignancy but may miss lesions <5 mm. The differentiation between bilateral micronodular hyperplasia and a unilateral adenoma is only required if a surgical approach is feasible and desired. Consequently, selective adrenal vein sampling (AVS) should only be carried out in

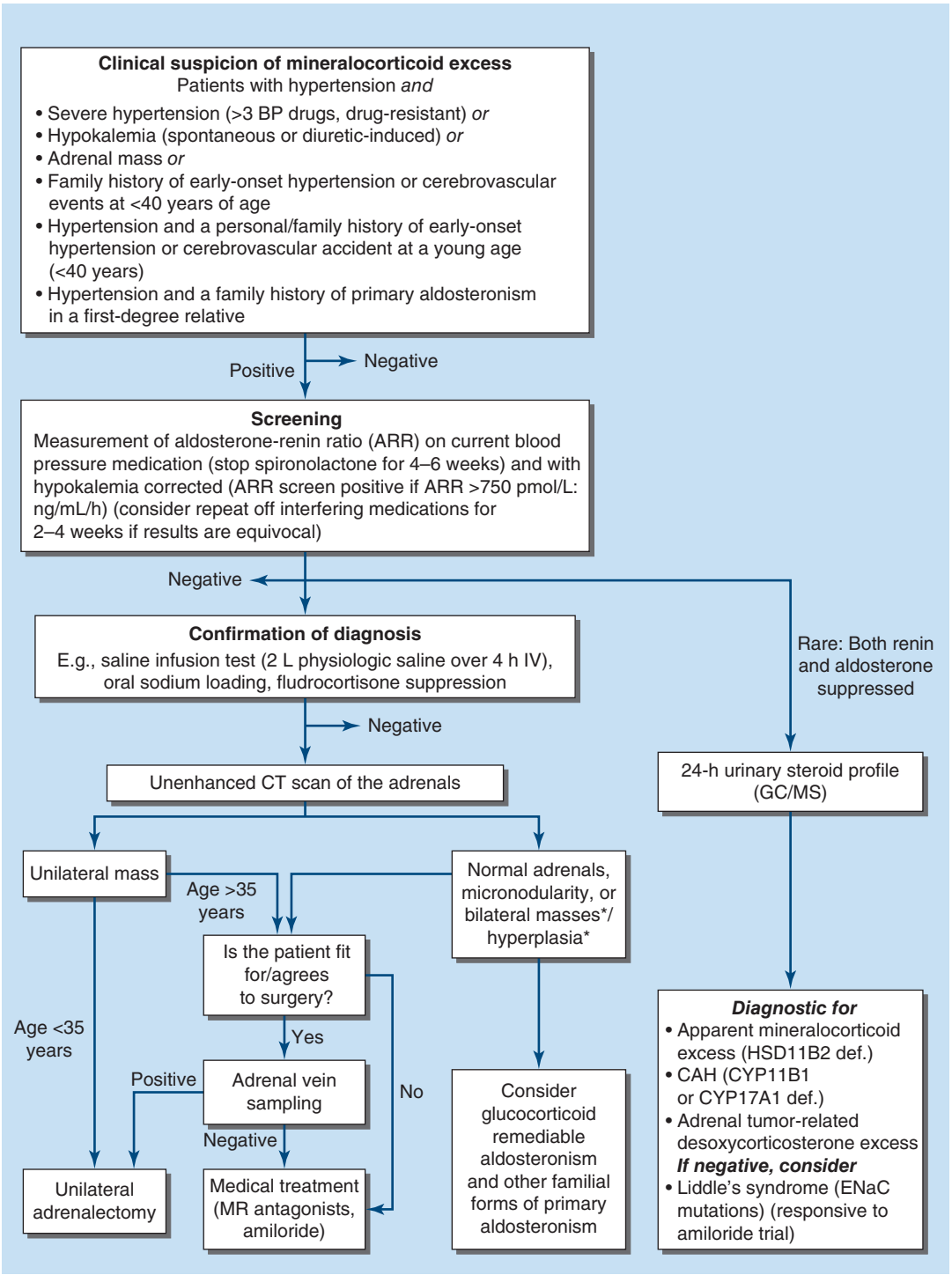

FIGURE 398-12 Management of patients with suspected mineralocorticoid excess. Perform adrenal tumor workup (see Fig. 398-13). BP, blood pressure; CAH, congenital adrenal hyperplasia; CT, computed tomography; ENaC, epithelial sodium channel; GC/MS, gas chromatography/mass spectrometry; MR, mineralocorticoid receptor; PRA, plasma renin activity.

TABLE 398-4 Effects of Medications and Other Conditions on the Aldosterone-Renin Ratio (ARR)

EFFECT ON THE ARR	ANTIHYPERTENSIVE DRUGS	OTHER MEDICATIONS	OTHER CONDITIONS
Possible *false-negative* results (due to increase of renin and/or aldosterone)	MR antagonists; diuretics; DHP-calcium antagonists; ACE inhibitors; AT1R blockers; aliskiren[a]	SGLT2 inhibitors; SSRIs	Hypokalemia; dietary salt restriction; malignant hypertension; renovascular hypertension; pregnancy
Possible *false-positive* results (due to reduction of renin and/or aldosterone)	β-Blockers; clonidine; α-methyldopa; aliskiren[a]	NSAIDs; estrogen-containing oral contraceptives	Impaired renal function with hyperkalemia; luteal phase of the menstrual cycle in premenopausal women
Negligible effect	Non-DHP-calcium antagonists; α_1-adrenergic receptor antagonists; hydralazine	/	/

[a]The direct renin inhibitor aliskiren can cause false-negative results if the direct renin concentration is measured, as it causes a reduction of plasma renin activity.

Abbreviations: ACE, angiotensin-converting enzyme; AT1R, angiotensin II receptor type 1; DHP, dihydropyridine; MR, mineralocorticoid receptor; NSAID, nonsteroidal anti-inflammatory drug; SGLT2, sodium-glucose cotransporter 2; SSRI, selective serotonin reuptake inhibitor.

surgical candidates with either no obvious lesion on CT or evidence of a unilateral lesion but with age >35 years because the latter patients have a higher likelihood of harboring a coincidental, endocrine-inactive adrenal adenoma (Fig. 398-12). AVS is used to compare aldosterone levels in the inferior vena cava and between the right and left adrenal veins. AVS requires concurrent measurement of cortisol to document the correct placement of the catheter in the adrenal veins and should demonstrate a cortisol gradient >2–3 in baseline conditions between the vena cava and each adrenal vein. Lateralization is confirmed by an aldosterone/cortisol ratio that is at least twofold higher on one side than the other in baseline conditions. AVS is a complex procedure that requires a highly skilled interventional radiologist. Even then, the right adrenal vein can be difficult to cannulate correctly, which, if not achieved, invalidates the procedure. There is also no agreement as to whether the two adrenal veins should be cannulated simultaneously or successively and whether ACTH stimulation enhances the diagnostic value of AVS. Recently, PET-CT with a labeled form of metomidate, a methyl analogue of etomidate that binds to both CYP11B1 and CYP11B2, has been validated as a noninvasive alternative to AVS. [^{11}C] metomidate PET-CT with dexamethasone pretreatment to suppress CYP11B1 activity can differentiate unilateral from bilateral forms of primary aldosteronism and has similar performance to AVS in predicting biochemical and clinical success following adrenalectomy.

Patients <35 years with confirmed primary aldosteronism, a unilateral lesion on CT, and no clinical suspicion of familial forms can go straight to surgery, which is also indicated in patients with confirmed lateralization documented by a valid AVS procedure or [^{11}C]metomidate PET-CT. Laparoscopic adrenalectomy is the preferred approach. Patients who are not surgical candidates, or with evidence of bilateral hyperplasia based on CT or AVS, should be treated medically (Fig. 398-12). Medical treatment, which can also be considered prior to surgery to avoid postsurgical hypoaldosteronism, consists primarily of the MR antagonist spironolactone. It can be started at 12.5–50 mg daily and titrated up to a maximum of 400 mg/d to control blood pressure and normalize potassium. Side effects include menstrual irregularity, decreased libido, and gynecomastia. The more selective MR antagonist eplerenone can also be used. Doses start at 25 mg bid, and it can be titrated up to 200 mg/d. Another useful drug is the potassium-sparing diuretic amiloride (5–10 mg bid).

In patients with normal adrenal morphology and family history of early-onset, severe hypertension, a diagnosis of GRA should be considered and can be evaluated using genetic testing. Treatment of GRA consists of administering dexamethasone, using the lowest dose possible to control blood pressure. Some patients also require additional MR antagonist treatment.

The diagnosis of non-aldosterone-related mineralocorticoid excess is based on documentation of suppressed renin and suppressed aldosterone in the presence of hypokalemic hypertension. This testing is best carried out by employing urinary steroid metabolite profiling by gas chromatography/mass spectrometry (GC/MS). An increased free cortisol over free cortisone ratio is suggestive of SAME and can be treated with dexamethasone. Steroid profiling by GC/MS also detects the steroids associated with CYP11B1 and CYP17A1 deficiency or the irregular steroid secretion pattern in a DOC-producing ACC (Fig. 398-12). If the GC/MS profile is normal, Liddle's syndrome should be considered. It is very sensitive to amiloride treatment but will not respond to MR antagonist treatment because the defect is due to a constitutively active ENaC.

APPROACH TO THE PATIENT: INCIDENTALLY DISCOVERED ADRENAL MASS

Epidemiology Incidentally discovered adrenal masses, commonly termed adrenal "incidentalomas," are common, with a prevalence of 2–5% in the general population as documented in CT and autopsy series. The prevalence increases with age, with 1% of 40-year-olds and 7% of 70-year-olds harboring an adrenal mass. The widespread use of cross-sectional imaging has also increased the recognized prevalence.

Etiology Most solitary adrenal tumors are monoclonal neoplasms. Several genetic syndromes, including MEN 1 (*MEN1*), MEN 2 (*RET*), Carney's complex (*PRKAR1A*), McCune-Albright (*GNAS1*), Li Fraumeni (*TP53*), Lynch (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), and familial adenomatous polyposis (*APC*) can have adrenocortical tumors as one of their features. On the other hand, Von-Hippel-Lindau disease (*VHL*), MEN 2, paraganglioma syndrome type 1/4/5 (*SDHD*/*SDHB*/*SDHA*), neurofibromatosis type 1 (*NF1*), and hereditary leiomyomatosis and renal cell cancer (*FH*) are among the genetic syndromes associated with pheochromocytomas.

TABLE 398-5 Classification of Unilateral Adrenal Masses

MASS	APPROXIMATE PREVALENCE (%)
Benign	
Adrenocortical adenoma	
Endocrine-inactive	40–70
Cortisol-producing (mild autonomous cortisol secretion)	20–50
Aldosterone-producing	2–5
Cortisol-producing (overt Cushing's syndrome)	1–4
Pheochromocytoma	1–5
Adrenal myelolipoma	3-6
Adrenal ganglioneuroma	1
Adrenal cyst and pseudocyst	1
Adrenal hematoma/hemorrhagic infarction	<1
Adrenal hemangioma	<0.1
Indeterminate	
Adrenocortical oncocytoma	<1
Malignant	
Metastases (most frequent: breast, lung)	3–7
Adrenocortical carcinoma	0.4–4
Malignant pheochromocytoma	<1
Adrenal neuroblastoma	<0.1
Lymphomas (including primary adrenal lymphoma)	<0.1

Note: Bilateral adrenal enlargement/masses may be caused by congenital adrenal hyperplasia, bilateral macronodular hyperplasia, bilateral hemorrhage (due to antiphospholipid syndrome or sepsis-associated Waterhouse-Friderichsen syndrome), granuloma, amyloidosis, or infiltrative disease including tuberculosis.

Up to 50% of adrenal nodules are hormonally active, due to a cortisol- or aldosterone-producing adrenocortical adenoma or a pheochromocytoma associated with catecholamine excess (Table 398-5). ACC is rare but is the cause of an adrenal mass in up to 4% of patients. However, metastases originating from another solid tissue tumor are an additional cause of adrenal incidentaloma and account for up to 40% of adrenal masses in patients undergoing imaging for tumor staging or follow-up monitoring (Table 398-5).

Differential Diagnosis and Treatment Patients with an adrenal mass >1 cm require a diagnostic evaluation. Two key questions need to be addressed: (1) Does the tumor autonomously secrete hormones that could have a detrimental effect on health? (2) Is the adrenal mass benign or malignant?

Hormone secretion by an adrenal mass occurs along a continuum, with a gradual increase in clinical manifestations in parallel with hormone levels. Exclusion of catecholamine excess from a pheochromocytoma arising from the adrenal medulla is a mandatory part of the diagnostic workup of lipid-poor masses (Fig. 398-13). In case of hypertension, primary aldosteronism should be ruled out. Overproduction of adrenal androgen precursors, DHEA and its sulfate, is rare and most frequently seen in the context of ACC, as are increased levels of steroid precursors such as 17OHP. Cortisol excess is the most observed hormonal abnormality in adrenal masses, ranging from rare clinically overt Cushing's syndrome to much more prevalent MACS (early-morning cortisol >50 nmol/L [1.8 μg/dL] after overnight administration of dexamethasone 1 mg in the absence of clinical features of Cushing's). Patients with MACS may exhibit one or more components of the metabolic syndrome (e.g., obesity, type 2 diabetes, hypertension,

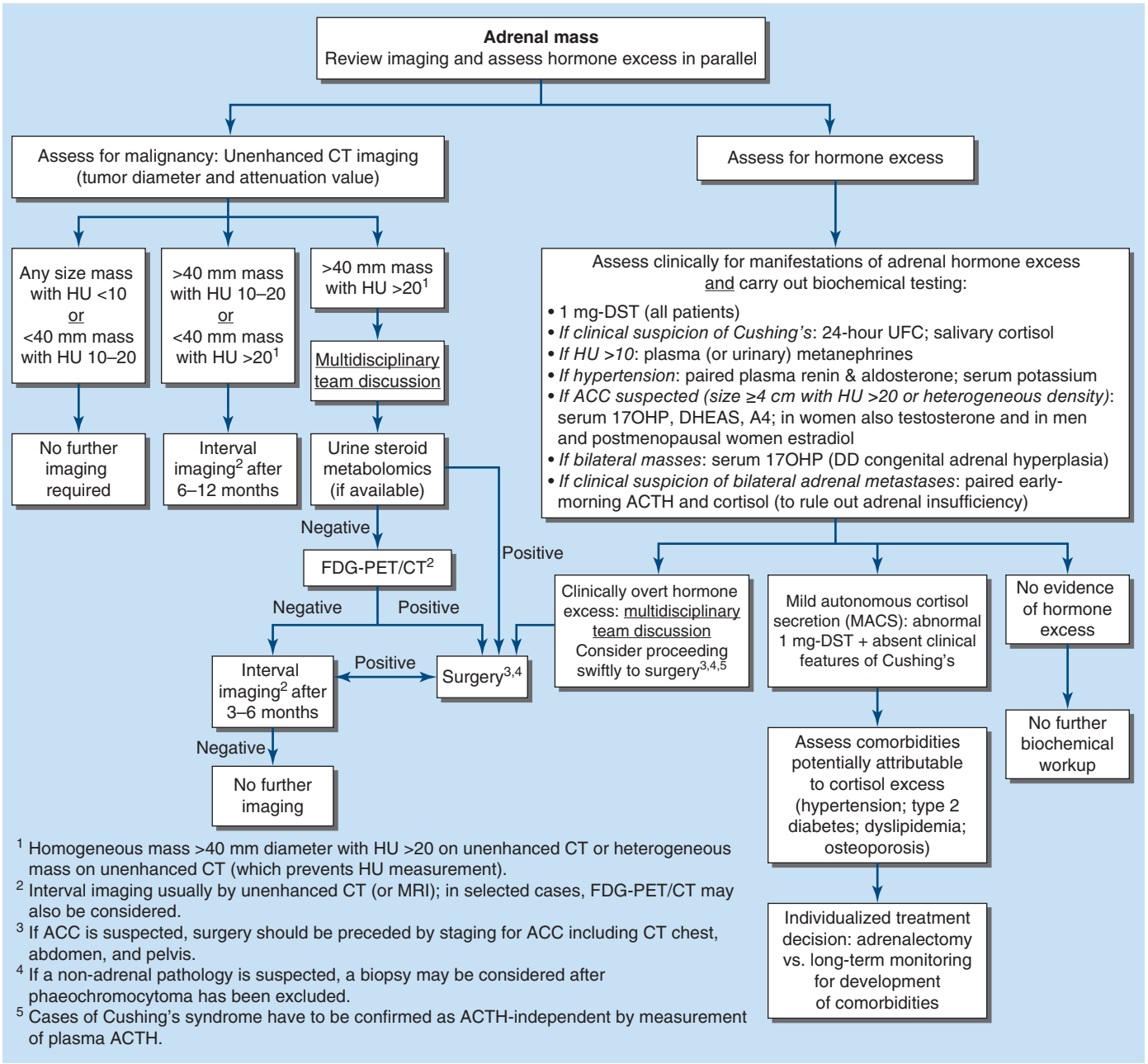

FIGURE 398-13 Management of the patient with an incidentally discovered adrenal mass. This pathway is primarily designed for adrenal incidentalomas; in adrenal nodules identified by screening or staging for an extra-adrenal primary malignancy, the likelihood of a metastasis needs to be considered when arranging further imaging or a biopsy. ACC, adrenocortical carcinoma; ACTH, adrenocorticotropic hormone; CT, computed tomography; DD, differential diagnosis; DHEAS, dehydroepiandrosterone sulfate; 1 mg-DST, 1 mg dexamethasone overnight suppression test; FDG-PET, fluorodeoxyglucose positron emission tomography; HU, Hounsfield Units; 17-OHP, 17-hydroxyprogesterone; MACS, mild autonomous cortisol excess secretion; MRI, magnetic resonance imaging; UFC, urinary free cortisol.

dyslipidemia), osteoporosis, increased risk of cardiovascular events, frailty, and impaired quality of life, and have increased mortality risk. There is an ongoing debate about the optimal treatment for these patients, which includes adrenalectomy or conservative management with long-term monitoring and treatment of comorbidities potentially attributable to the cortisol excess.

For the differentiation of benign from malignant adrenal masses, imaging is relatively sensitive, although specificity is suboptimal. Unenhanced CT is the procedure of choice for imaging the adrenal glands (Fig. 398-11). A diagnosis of ACC, pheochromocytoma, and benign adrenal myelolipoma becomes more likely with increasing diameter of the adrenal mass. However, size alone is of poor predictive value, with only 80% specificity for the differentiation of benign from malignant masses when using a 4-cm cutoff. Metastases are rare but are found with similar frequency in adrenal masses of all sizes. The tumor attenuation value on unenhanced CT is of high diagnostic value, as many adrenocortical adenomas are lipid rich and thus present with low attenuation values (i.e., densities of <20 HUs). However, similar numbers of adrenocortical adenomas are lipid poor and present with higher HUs, making it difficult to differentiate them from ACCs, as well as pheochromocytomas, both of which invariably have high attenuation values (i.e., densities >20 HU on precontrast scans). Generally, benign lesions are rounded and homogenous, whereas most malignant lesions appear lobulated and inhomogeneous. Pheochromocytoma and adrenomyelolipoma may also exhibit lobulated and inhomogeneous features. MRI also allows for the visualization of the adrenal glands with somewhat lower resolution than CT. However, because it does not involve exposure to ionizing radiation, it is preferred in children, young adults, and during pregnancy. MRI has a valuable role in the characterization of indeterminate adrenal lesions using chemical shift analysis, with malignant tumors rarely showing loss of signal on opposed-phase MRI; however, this may also be observed in a proportion of benign

adrenocortical adenomas, and chemical shift analysis results usually are similar to those obtained by measuring tumor attenuation on unenhanced CT. The evidence base for the utility of fluorodeoxyglucose (FDG)-PET was initially scarce but is now expanding, with recent data indicating that a lack of FDG uptake reliably indicates a benign adrenocortical mass; however, care has to be taken in patients with a history of extra-adrenal cancer as adrenal metastases arising from those sometimes do not take up FDG, i.e., as typically seen in renal cell carcinoma. Adrenocortical carcinoma is invariably FDG avid; however, specificity is poor, with many benign adrenal adenomas also taking up FDG.

Fine-needle aspiration (FNA) or CT-guided biopsy of an adrenal mass is very rarely indicated. FNA of a pheochromocytoma can cause a life-threatening hypertensive crisis. FNA of an ACC violates the tumor capsule and can cause needle track metastasis. FNA should only be considered in a patient with a history of nonadrenal malignancy and a newly detected adrenal mass, after careful exclusion of pheochromocytoma, and if the outcome will influence therapeutic management. It is important to recognize that in 25% of patients with a previous history of nonadrenal malignancy, a newly detected mass on CT is not a metastasis. While FNA can diagnose extra-adrenal malignancies, it has very limited ability to differentiate between benign and malignant adrenocortical lesions and hence should not be used for the diagnosis of ACC.

Adrenal masses associated with confirmed hormone excess or suspected malignancy are usually treated surgically (Fig. 398-13) or, if adrenalectomy is not feasible or desired, with medication. Preoperative exclusion of glucocorticoid excess is particularly important for the prediction of postoperative suppression of the contralateral adrenal gland, which requires glucocorticoid replacement peri- and postoperatively. Adrenal masses of any size with normal endocrine biochemistry at diagnosis and an attenuation value of <10 HU on unenhanced CT can be considered benign (malignancy rate <0.5%) and do not require further follow-up (Fig. 398-13). This similarly applies to adrenal masses <4 cm in diameter and an attenuation value of 10–20 HU. In adrenal masses <4 cm and >20 HU attenuation as well as in masses >4 cm and 10–20 HU, the likelihood of malignancy is still very low (<5%) and can be mitigated by arranging for interval imaging (Fig. 398-13). The overwhelming majority of risk of malignancy applies to adrenal masses >4 cm with an attenuation >20 HU, and these masses require swift attention (Fig. 398-13), with a 50% risk of underlying malignancy. The risk of adrenocortical carcinoma is higher in young patients (<40 years), whereas metastases of extra-adrenal primaries occur at all ages. In adrenal masses with suspicious imaging findings (>4 cm and >20 HU), surgery and/or biopsy are feasible options; however, the latter will still result in unnecessary surgery for many benign tumors. A recently introduced diagnostic test, urine steroid metabolomics, has a twofold higher positive predictive value than imaging in detecting adrenocortical carcinoma, based on a distinct "malignant steroid fingerprint" with accumulating precursor steroid metabolites in 24-h urine.

ADRENOCORTICAL CARCINOMA

ACC is a rare malignancy with an annual incidence of 1–2 per million population. ACC is generally considered a highly malignant tumor; however, it presents with broad interindividual variability with regard to biologic characteristics and clinical behavior. Somatic mutations in the tumor-suppressor gene *TP53* are found in 25% of apparently sporadic ACC. Germline *TP53* mutations are the cause of the Li-Fraumeni syndrome associated with multiple solid organ cancers including ACC and are found in 25% of pediatric ACC cases; the *TP53* mutation R337H is found in almost all pediatric ACC in Brazil. Other genetic changes identified in ACC include germline mutations of genes affecting DNA mismatch repair (Lynch syndrome), *PRKAR1A* (Carney complex), *MEN1*, *APC* (familial adenomatous polyposis), and somatic alterations in the Wnt/β-catenin pathway and in the insulin-like growth factor 2 (IGF2) cluster. IGF2 overexpression is found in 90% of ACCs.

Patients with large adrenal tumors suspicious of malignancy should be managed by a multidisciplinary specialist team, including an endocrinologist, an oncologist, a surgeon, a radiologist, and a histopathologist. FNA is not indicated in suspected ACC: first, cytology and also histopathology of a core biopsy cannot differentiate between benign and malignant primary adrenal masses; second, FNA violates the tumor capsule and may even cause needle canal metastasis. Even when the entire tumor specimen is available, the histopathologic differentiation between benign and malignant adrenocortical lesions is a diagnostic challenge. The most common histopathologic classification is the Weiss score, taking into account high nuclear grade; mitotic rate (>5/high-power field [HPF]); atypical mitosis; <25% clear cells; diffuse architecture; and presence of necrosis, venous invasion, and invasion of sinusoidal structures and tumor capsule. The presence of three or more elements suggests ACC. However, FNA is a feasible option if looking for metastases of an extra-adrenal primary or other adrenal tumor entities, such as ganglioneuroma.

TABLE 398-6 Classification System for Staging of Adrenocortical Carcinoma

ENSAT STAGE	TNM STAGE	TNM DEFINITIONS
I	T1,N0,M0	T1, tumor ≤5 cm N0, no positive lymph node M0, no distant metastases
II	T2,N0,M0	T2, tumor >5 cm N0, no positive lymph node M0, no distant metastases
III	T1–T2,N1,M0 T3–T4,N0–N1,M0	N1, positive lymph node(s) M0, no distant metastases T3, tumor infiltration into surrounding tissue T4, tumor invasion into adjacent organs *or* venous tumor thrombus in vena cava or renal vein
IV	T1–T4,N0–N1,M1	M1, presence of distant metastases

Abbreviations: ENSAT, European Network for the Study of Adrenal Tumors; TNM, tumor, node, metastasis.

Although 60–70% of ACCs show biochemical evidence of steroid overproduction, in many patients, this is not clinically apparent due to the relatively inefficient steroid production by the adrenocortical cancer cells. Excess production of glucocorticoids and adrenal androgen precursors are most common and indicative of malignancy.

Tumor staging at ACC diagnosis **(Table 398-6)** has important prognostic implications and requires scanning of the chest and abdomen for local organ invasion, lymphadenopathy, and metastases. Intravenous contrast medium is necessary for maximum sensitivity for hepatic metastases. An adrenal origin may be difficult to determine on standard axial CT imaging if the tumors are large and invasive, but CT reconstructions and MRI are more informative **(Fig. 398-14)** using multiple planes and different sequences. Vascular and adjacent organ invasion is diagnostic of malignancy. 18-Fluoro-2-deoxy-D-glucose PET (18-FDG-PET) is highly sensitive for the detection of malignancy and can be used to detect small metastases or local recurrence that may not be obvious on CT (Fig. 398-14). However, FDG-PET has limited specificity and therefore cannot be used for differentiating benign from malignant adrenal lesions. Metastasis in ACC most frequently occurs to liver and lung.

There is no established grading system for ACC, and the Weiss score carries no prognostic value; the most important prognostic histopathologic parameter is the Ki67 proliferation index, with Ki67 <10% indicative of slow to moderate growth velocity, whereas a Ki67 ≥10% is associated with poor prognosis including high risk of recurrence and rapid progression.

Cure of ACC can only be achieved by early detection and complete surgical removal. Capsule violation during primary surgery, metastasis at diagnosis, and primary treatment in a nonspecialist center and by a nonspecialist surgeon are major determinants of poor survival. If the primary tumor invades adjacent organs, en bloc removal of kidney and spleen should be considered to reduce the risk of recurrence, and regional lymph node dissection may further reduce this risk. Surgery

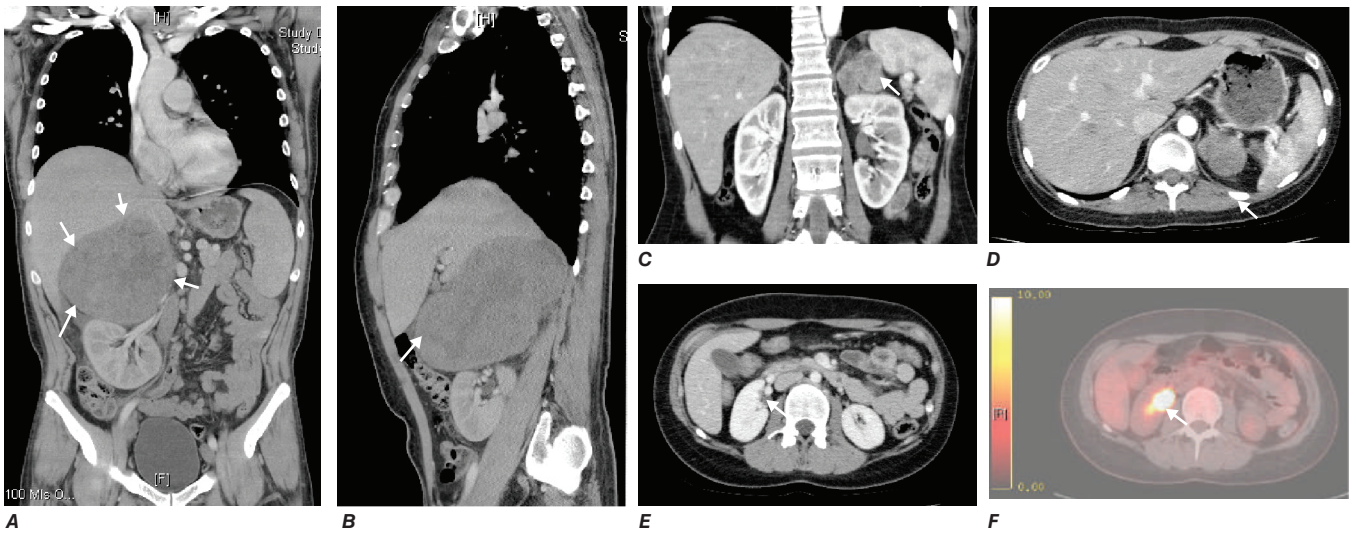

FIGURE 398-14 Imaging in adrenocortical carcinoma (ACC). Magnetic resonance imaging scan with (***A***) frontal and (***B***) lateral views of a right ACC that was detected incidentally. Computed tomography (CT) scan with (***C***) coronal and (***D***) transverse views depicting a right-sided ACC. Note the irregular border and inhomogeneous structure. CT scan (***E***) and positron emission tomography/CT (***F***) visualizing a peritoneal metastasis of an ACC in close proximity to the right kidney (*arrow*).

can also be considered in a patient with metastases if there is severe tumor-related hormone excess. This indication needs to be carefully weighed against surgical risk, including thromboembolic complications, and the resulting delay in the introduction of other therapeutic options. Patients with confirmed ACC and successful removal of the primary tumor should receive adjuvant treatment with mitotane (o,p'DDD), particularly in patients with a high risk of recurrence as determined by European Network for the Study of Adrenal Tumors (ENSAT) stage III and IV or Ki67 proliferation index ≥10%. Adjuvant mitotane should be continued for at least 2 years, if side effects are tolerated. Regular monitoring of plasma mitotane levels is mandatory (therapeutic range 14–20 mg/L; neurotoxic complications more frequent at >20 mg/L). Mitotane is usually started at 500 mg tid, with stepwise increases to a maximum dose of 2000 mg tid in days (high-dose saturation) or weeks (low-dose saturation) as tolerated. Once therapeutic range plasma mitotane levels are achieved, the dose can be tapered to maintenance doses mostly ranging from 1000 to 1500 mg tid. Mitotane treatment results in disruption of cortisol synthesis and thus requires glucocorticoid replacement; glucocorticoid replacement dose should be at least double of that usually used in adrenal insufficiency (i.e., 40–60 mg daily in two to three divided doses) because mitotane induces hepatic CYP3A4 activity, resulting in rapid inactivation of glucocorticoids. Mitotane also increases circulating CBG, thereby decreasing the available free cortisol fraction. Single metastases can be addressed surgically or with radiofrequency ablation as appropriate. If the tumor recurs or progresses during mitotane treatment, cytotoxic chemotherapy should be considered; the established first-line chemotherapy regimen is the combination of cisplatin, etoposide, and doxorubicin plus continuing mitotane. Painful bone metastasis responds to irradiation. Overall survival in ACC is still poor, with 5-year survival rates of 30–40% and a median survival of 15 months in metastatic ACC.

ADRENAL INSUFFICIENCY

Epidemiology The prevalence of well-documented, permanent adrenal insufficiency is 5 in 10,000 in the general population. Hypothalamic-pituitary origin of the disease is most frequent, with a prevalence of 3 in 10,000, whereas primary adrenal insufficiency has a prevalence of 2 in 10,000. Approximately one-half of the latter cases are acquired, mostly caused by autoimmune destruction of the adrenal glands; the other one-half are genetic, most commonly caused by distinct enzymatic blocks in adrenal steroidogenesis affecting glucocorticoid synthesis (i.e., CAH).

Adrenal insufficiency arising from suppression of the HPA axis consequent to exogenous glucocorticoid treatment is much more common, occurring in 0.5–2% of the population in developed countries.

Etiology *Primary adrenal insufficiency* is most commonly caused by autoimmune adrenalitis. Isolated autoimmune adrenalitis accounts for 30–40%, whereas 60–70% develop adrenal insufficiency as part of autoimmune polyglandular syndromes (APSs) **(Chap. 400)** **(Table 398-7)**. APS1, also termed APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), is the underlying cause in 10% of patients affected by APS. APS1 is transmitted in an autosomal recessive manner and is caused by mutations in the autoimmune regulator gene *AIRE*. Associated autoimmune conditions overlap with those seen in APS2 but may also include total alopecia, primary hypoparathyroidism, and, in rare cases, lymphoma. APS1 patients invariably develop chronic mucocutaneous candidiasis, usually manifested in childhood and preceding adrenal insufficiency by years or decades. The much more prevalent APS2 is of polygenic inheritance, with confirmed associations with the *HLA-DR3* gene region in the major histocompatibility complex and distinct gene regions involved in immune regulation (*CTLA-4, PTPN22, CLEC16A*). Coincident autoimmune disease most frequently includes thyroid autoimmune disease, vitiligo, and premature ovarian failure. Less commonly, additional features may include type 1 diabetes and pernicious anemia caused by vitamin B_{12} deficiency.

X-linked adrenoleukodystrophy has an incidence of 1:20,000 males and is caused by mutations in the *X-ALD* gene encoding the peroxisomal membrane transporter protein ABCD1; its disruption results in the accumulation of very-long-chain (>24 carbon atoms) fatty acids. Approximately 50% of cases manifest in early childhood with rapidly progressive white matter disease (cerebral adrenoleukodystrophy); 35% present during adolescence or in early adulthood with neurologic features indicative of myelin and peripheral nervous system involvement (adrenomyeloneuropathy [AMN]). In the remaining 15%, adrenal insufficiency is the sole manifestation of disease. Of note, distinct mutations manifest with variable penetrance and phenotypes within affected families.

Rarer causes of adrenal insufficiency involve the destruction of the adrenal glands as a consequence of infection, hemorrhage, or infiltration (Table 398-7); tuberculous adrenalitis is still a frequent cause of disease in developing countries. Adrenal metastases rarely cause adrenal insufficiency, and this occurs only with bilateral, bulky metastases.

Inborn causes of primary adrenal insufficiency other than CAH are rare, causing <1% of cases. However, their elucidation provides important insights into adrenal gland development and physiology. Mutations causing primary adrenal insufficiency (Table 398-7) include factors regulating adrenal development and steroidogenesis (DAX-1, SF-1), cholesterol synthesis, import and cleavage (DHCR7, StAR, CYP11A1), elements of the adrenal ACTH response pathway (MC2R, MRAP) (Fig. 398-5), and factors involved in redox regulation (NNT, TXNRD2) and DNA repair (MCM4, CDKN1C).

TABLE 398-7 Causes of Primary Adrenal Insufficiency

DIAGNOSIS	GENE	ASSOCIATED FEATURES
Autoimmune polyglandular syndrome 1 (APS1)	*AIRE*	Hypoparathyroidism, chronic mucocutaneous candidiasis, other autoimmune disorders, rarely lymphomas
Autoimmune polyglandular syndrome 2 (APS2)	Associations with HLA-DR3, CTLA-4	Hypothyroidism, hyperthyroidism, premature ovarian failure, vitiligo, type 1 diabetes mellitus, pernicious anemia
Isolated autoimmune adrenalitis	Associations with HLA-DR3, CTLA-4	
Congenital adrenal hyperplasia (CAH)	*CYP21A2, CYP11B1, CYP17A1, HSD3B2, POR*	See Table 398-10 (see also **Chap. 402**)
Congenital lipoid adrenal hyperplasia (CLAH)	*STAR, CYP11A1*	46,XY DSD, gonadal failure (see also **Chap. 402**)
Adrenal hypoplasia congenita (AHC)	*NR0B1 (DAX-1), NR5A1 (SF-1)*	46,XY DSD, gonadal failure (see also **Chap. 402**)
Adrenoleukodystrophy (ALD), adrenomyeloneuropathy (AMN)	*ABCD1*	Demyelination of central nervous system (ALD) or spinal cord and peripheral nerves (AMN)
Familial glucocorticoid deficiency	*MC2R*	Tall stature
	MRAP	None
	STAR	None
	NNT	None
	TXNRD2	None
	MCM4	Growth retardation, natural killer cell deficiency
Triple A syndrome	*AAAS*	Alacrima, achalasia, neurologic impairment
Smith-Lemli-Opitz syndrome	*SLOS*	Cholesterol synthesis disorder associated with mental retardation, craniofacial malformations, growth failure
Kearns-Sayre syndrome	Mitochondrial DNA deletions	Progressive external ophthalmoplegia, pigmentary retinal degeneration, cardiac conduction defects, gonadal failure, hypoparathyroidism, type 1 diabetes,
IMAGe syndrome	*CDKN1C*	Intrauterine growth retardation, metaphyseal dysplasia, genital anomalies
MIRAGE syndrome	*SAMD9*	Myelodysplasia, infection, restriction of growth, genital phenotypes, and enteropathy
Sphingosine-1-phosphate lyase deficiency	*SGPL1*	Steroid-resistant nephrotic syndrome, immunodeficiency, neurologic defects, ichthyosis, primary hypothyroidism, cryptorchidism
Adrenal infections		Tuberculosis, HIV, CMV, cryptococcosis, histoplasmosis, coccidioidomycosis
Adrenal infiltration		Metastases, lymphomas, sarcoidosis, amyloidosis, hemochromatosis
Adrenal hemorrhage		Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome
Drug-induced		Mitotane, aminoglutethimide, abiraterone, trilostane, etomidate, ketoconazole, levoketoconazole, osilodrostat, suramin, mifepristone (RU486), interferon-alpha, immune checkpoint inhibitors (rare)
Bilateral adrenalectomy		E.g., in the management of Cushing's syndrome or after bilateral nephrectomy

Abbreviations: AIRE, autoimmune regulator; CMV, cytomegalovirus; DSD, disordered sex development; MC2R, ACTH receptor; MCM4, mini chromosome maintenance-deficient 4 homologue; MRAP, MC2R-accessory protein; NNT, nicotinamide nucleotide transhydrogenase.

Secondary (or central) adrenal insufficiency is the consequence of dysfunction of the hypothalamic-pituitary component of the HPA axis **(Table 398-8)**. Excluding iatrogenic suppression, the overwhelming majority of cases are caused by pituitary or hypothalamic tumors or their treatment by surgery or irradiation **(Chap. 392)**. Rarer causes include pituitary apoplexy, either as a consequence of an infarcted pituitary adenoma or transient reduction in the blood supply of the pituitary during surgery or after rapid blood loss associated with parturition, also termed Sheehan's syndrome. Isolated ACTH deficiency is rarely caused by autoimmune disease or pituitary infiltration (Table 398-8). Mutations in the ACTH precursor POMC or in factors regulating pituitary development are genetic causes of ACTH deficiency (Table 398-8).

Clinical Manifestations In principle, the clinical features of primary adrenal insufficiency (Addison's disease) are characterized by the loss of both glucocorticoid and mineralocorticoid secretion **(Table 398-9)**. In secondary adrenal insufficiency, only glucocorticoid deficiency is present, as the adrenal itself is intact and thus still amenable to regulation by the RAA system. Adrenal androgen secretion is disrupted in both primary and secondary adrenal insufficiency (Table 398-9). Hypothalamic-pituitary disease can lead to additional clinical manifestations due to involvement of other endocrine axes (thyroid, gonads, GH, prolactin) or visual impairment with bitemporal hemianopia caused by chiasmal compression. It is important to recognize that iatrogenic adrenal insufficiency caused by exogenous glucocorticoid suppression of the HPA axis may result in all symptoms associated with glucocorticoid deficiency (Table 398-9), if exogenous glucocorticoids are stopped abruptly. However, patients will appear clinically cushingoid as a result of the preceding overexposure to glucocorticoids.

Chronic adrenal insufficiency manifests with relatively nonspecific signs and symptoms, such as fatigue and loss of energy, often resulting in delayed or missed diagnoses (e.g., as depression or anorexia). A distinguishing feature of primary adrenal insufficiency is hyperpigmentation, which is caused by excess ACTH stimulation of melanocytes. Hyperpigmentation is most pronounced in skin areas exposed to increased friction or shear stress and is increased by sunlight **(Fig. 398-15)**. Conversely, in secondary adrenal insufficiency, the skin has an alabaster-like paleness due to lack of ACTH secretion.

Hyponatremia is a characteristic biochemical feature in primary adrenal insufficiency and is found in 80% of patients at presentation. Hyperkalemia is present in 40% of patients at initial diagnosis. Hyponatremia is primarily caused by mineralocorticoid deficiency but can also occur in secondary adrenal insufficiency due to diminished inhibition of antidiuretic hormone (ADH) release by cortisol, resulting in mild syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Glucocorticoid deficiency also results in slightly increased TSH concentrations that normalize within days to weeks after initiation of glucocorticoid replacement.

TABLE 398-8 Causes of Secondary Adrenal Insufficiency

DIAGNOSIS	GENE	ASSOCIATED FEATURES
Pituitary tumors (endocrine active and inactive adenomas, very rare: carcinoma)		Depending on tumor size and location: visual field impairment (bilateral hemianopia), hyperprolactinemia, secondary hypothyroidism, hypogonadism, growth hormone deficiency
Other mass lesions affecting the hypothalamic-pituitary region		Craniopharyngioma, meningioma, ependymoma, metastases
Pituitary irradiation		Radiotherapy administered for pituitary tumors, brain tumors, or craniospinal irradiation in leukemia
Autoimmune hypophysitis		Often associated with pregnancy; may present with panhypopituitarism or isolated ACTH deficiency; can be associated with autoimmune thyroid disease, more rarely with vitiligo, premature ovarian failure, type 1 diabetes, pernicious anemia
Pituitary apoplexy/ hemorrhage		Hemorrhagic infarction of large pituitary adenomas or pituitary infarction consequent to traumatic major blood loss (e.g., surgery or pregnancy: Sheehan's syndrome)
Pituitary infiltration		Tuberculosis, actinomycosis, sarcoidosis, histiocytosis X, granulomatosis with polyangiitis (Wegener's), metastases
Drug-induced		Chronic glucocorticoid excess (endogenous or exogenous), immune check point inhibitors, opioids, interferon alpha, ribavirin, megestrol acetate
Congenital isolated ACTH deficiency	*TBX19* (Tpit)	
Combined pituitary hormone deficiency (CPHD)	*PROP-1*	Progressive development of CPHD in the order GH, PRL, TSH, LH/FSH, ACTH
	HESX1	CPHD and septo-optic dysplasia
	LHX3	CPHD and limited neck rotation, sensorineural deafness
	LHX4	CPHD and cerebellar abnormalities
	SOX3	CPHD and variable mental retardation
Proopiomelanocortin (POMC) deficiency	*POMC*	Early-onset obesity, red hair pigmentation

Abbreviations: ACTH, adrenocorticotropic hormone; GH, growth hormone; LH/FSH, luteinizing hormone/follicle-stimulating hormone; PRL, prolactin; TSH, thyroid-stimulating hormone.

TABLE 398-9 Signs and Symptoms of Adrenal Insufficiency

Signs and Symptoms Caused by Glucocorticoid Deficiency
Fatigue, lack of energy
Weight loss, anorexia
Myalgia, joint pain
Fever
Normochromic anemia, lymphocytosis, eosinophilia
Slightly increased TSH (due to loss of feedback inhibition of TSH release)
Hypoglycemia (more frequent in children)
Low blood pressure, postural hypotension
Hyponatremia (due to loss of feedback inhibition of AVP release)
Signs and Symptoms Caused by Mineralocorticoid Deficiency (Primary Adrenal Insufficiency Only)
Abdominal pain, nausea, vomiting
Dizziness, postural hypotension
Salt craving
Low blood pressure, postural hypotension
Increased serum creatinine (due to volume depletion)
Hyponatremia
Hyperkalemia
Signs and Symptoms Caused by Adrenal Androgen Deficiency
Lack of energy
Dry and itchy skin (in women)
Loss of libido (in women)
Loss of axillary and pubic hair (in women)
Other Signs and Symptoms
Hyperpigmentation (primary adrenal insufficiency only) (due to excess of proopiomelanocortin [POMC]-derived peptides)
Alabaster-colored pale skin (secondary adrenal insufficiency only) (due to deficiency of POMC-derived peptides)

Abbreviations: AVP, arginine vasopressin; TSH, thyroid-stimulating hormone.

Acute adrenal insufficiency, also termed adrenal crisis, usually occurs after a prolonged period of nonspecific complaints and is more frequently observed in patients with primary adrenal insufficiency, due to the loss of both glucocorticoid and mineralocorticoid secretion. Postural hypotension may progress to hypovolemic shock. Adrenal insufficiency may mimic features of acute abdomen with abdominal tenderness, nausea, vomiting, and fever. In some cases, the primary presentation may resemble neurologic disease, with decreased responsiveness progressing to stupor and coma. An adrenal crisis can be triggered by an intercurrent illness, surgical or other stress, or increased glucocorticoid inactivation (e.g., hyperthyroidism). Prospective data indicate 8.3 adrenal crises and 0.5 adrenal crisis–related deaths per 100 patient-years.

Diagnosis The diagnosis of adrenal insufficiency is established by the short cosyntropin test, a safe and reliable tool with excellent predictive diagnostic value **(Fig. 398-16)**. The cutoff for failure is usually defined at cortisol levels of <450–500 nmol/L (16–18 μg/dL) sampled 30–60 min after ACTH stimulation; the exact cutoff is dependent on the locally available assay, with generally lower cutoffs for mass spectrometry–based assays. During the early phase of HPA disruption (e.g., within 4 weeks of pituitary insufficiency), patients may still respond to exogenous ACTH stimulation. In this circumstance, the ITT is an alternative choice but is more invasive and should be carried out only under a specialist's supervision (see above). Induction of hypoglycemia is contraindicated in individuals with diabetes mellitus, cardiovascular disease, or history of seizures. Random serum cortisol measurements are of limited diagnostic value because baseline cortisol levels may be coincidentally low due to the physiologic diurnal rhythm of cortisol secretion (Fig. 398-3). Similarly, many patients with secondary adrenal insufficiency have relatively normal baseline cortisol levels but fail to mount an appropriate cortisol response to ACTH, which can only be revealed by stimulation testing. Importantly, tests to establish the diagnosis of adrenal insufficiency should never delay treatment. Thus, in a patient with suspected adrenal crisis, it is reasonable to draw baseline cortisol levels, provide replacement therapy, and defer formal stimulation testing until a later time.

Once adrenal insufficiency is confirmed, measurement of plasma ACTH is the next step, with increased or inappropriately low levels defining primary and secondary origin of disease, respectively (Fig. 398-16). In primary adrenal insufficiency, increased plasma renin will confirm the presence of mineralocorticoid deficiency. At initial presentation, patients with primary adrenal insufficiency should undergo screening for steroid autoantibodies as a marker of autoimmune adrenalitis. If these tests are negative, adrenal imaging by CT is indicated to investigate possible hemorrhage, infiltration, or masses. In male patients with negative autoantibodies in the plasma, very-long-chain fatty acids should be measured to exclude X-ALD. Patients with inappropriately low ACTH, in the presence of confirmed cortisol deficiency, should undergo hypothalamic-pituitary imaging by MRI. Features suggestive of preceding pituitary apoplexy, such as sudden-onset severe headache or history of previous head trauma, should be carefully explored, particularly in patients with no obvious MRI lesion.

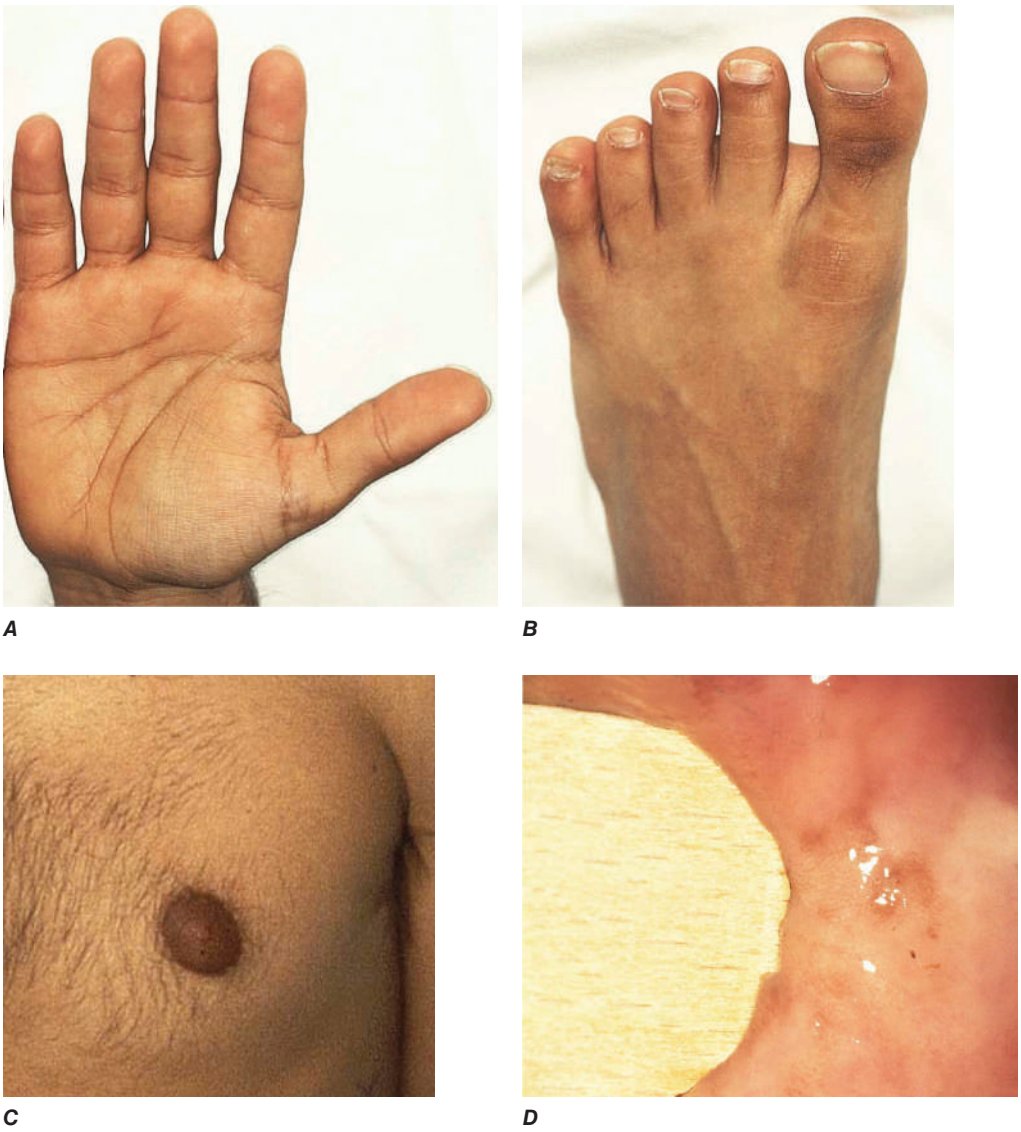

FIGURE 398-15 Clinical features of Addison's disease. Note the hyperpigmentation in areas of increased friction including (***A***) palmar creases, (***B***) dorsal foot, (***C***) nipples and axillary region, and (***D***) patchy hyperpigmentation of the oral mucosa.

TREATMENT

Acute Adrenal Insufficiency

Acute adrenal insufficiency requires immediate initiation of rehydration, usually carried out by saline infusion at initial rates of 1 L/h with continuous cardiac monitoring. Glucocorticoid replacement should be initiated by bolus injection of 100 mg hydrocortisone, followed by the administration of 200 mg hydrocortisone over 24 h, preferably by continuous infusion or alternatively by bolus IV or IM injections. Mineralocorticoid replacement can be initiated once the daily hydrocortisone dose has been reduced to <50 mg because at higher doses hydrocortisone provides sufficient stimulation of MRs.

Glucocorticoid replacement for the treatment of chronic adrenal insufficiency should be administered at a dose that replaces the physiologic daily cortisol production, which is usually achieved by the oral administration of 15–25 mg hydrocortisone in two to three divided doses. Pregnancy may require an increase in hydrocortisone dose by 50% during the last trimester. In all patients, at least one-half of the daily dose should be administered in the morning upon awakening. Long-acting glucocorticoids such as prednisolone or dexamethasone are not preferred because they result in increased glucocorticoid exposure due to extended GR activation at times of physiologically low cortisol secretion. There are no well-established dose equivalencies, but as a guide, equipotency can be assumed for 1 mg hydrocortisone, 1.6 mg cortisone acetate, 0.2 mg prednisolone, 0.25 mg prednisone, and 0.025 mg dexamethasone. Currently available standard glucocorticoid preparations fail to mimic the physiologic cortisol secretion rhythm (Fig. 398-3). However, this is overcome by recent modified release hydrocortisone preparations, with promising results emerging from the treatment of patients with primary adrenal insufficiency due to congenital adrenal hyperplasia.

Monitoring of glucocorticoid replacement is mainly based on the history and examination for signs and symptoms suggestive of glucocorticoid over- or underreplacement, including assessment of body weight and blood pressure. Plasma ACTH, 24-h urinary free cortisol, or serum cortisol day curves reflect whether hydrocortisone has been taken or not but do not convey reliable information about replacement quality. In patients with isolated primary adrenal insufficiency, monitoring should include screening for autoimmune thyroid disease, and female patients should be made aware of the possibility of premature ovarian failure. Supraphysiologic glucocorticoid treatment with doses equivalent to 30 mg hydrocortisone or more will affect bone metabolism, and these patients should undergo regular bone mineral density evaluation. All patients with adrenal insufficiency need to be instructed about the requirement for stress-related glucocorticoid dose adjustments. These generally consist of doubling the routine oral glucocorticoid dose in the case of intercurrent illness with fever and bed rest and the need for immediate IV or IM injection of 100 mg hydrocortisone followed

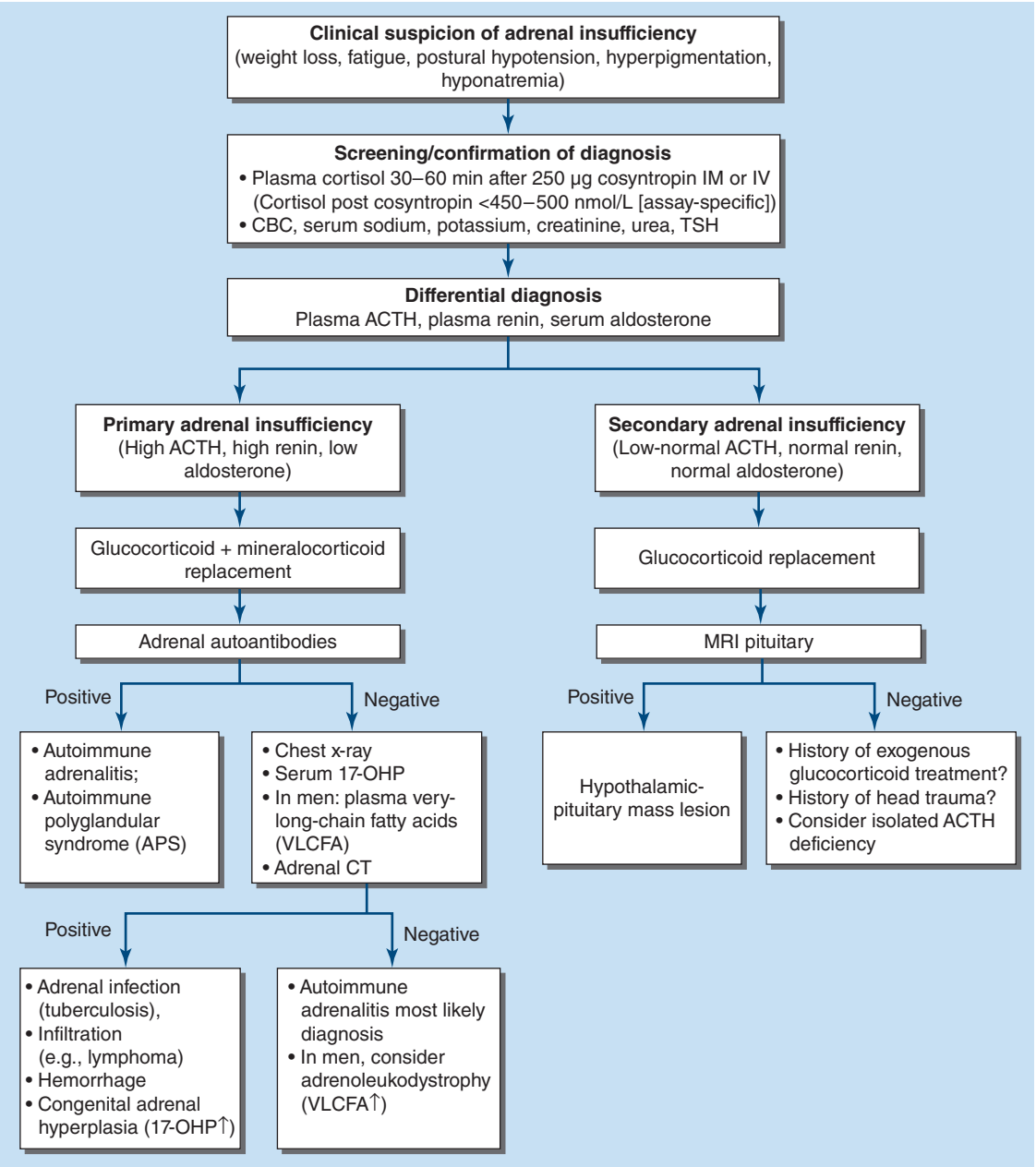

FIGURE 398-16 Management of the patient with suspected adrenal insufficiency. ACTH, adrenocorticotropic hormone; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; 17-OHP, 17-hydroxyprogesterone; PRA, plasma renin activity; TSH, thyroid-stimulating hormone.

by intravenous infusion of 200 mg hydrocortisone/24 h in cases of prolonged vomiting, surgery, or trauma. All patients, but in particular those living or traveling in regions with delayed access to acute health care, should carry a hydrocortisone self-injection emergency kit, in addition to their usual steroid emergency cards and bracelets, and should receive training in its use.

Mineralocorticoid replacement in primary adrenal insufficiency should be initiated at a dose of 100–150 µg fludrocortisone. The adequacy of treatment can be evaluated by measuring blood pressure, sitting and standing, to detect a postural drop indicative of hypovolemia. In addition, serum sodium, potassium, and plasma renin should be measured regularly. Renin levels should be kept in the upper normal reference range. Changes in glucocorticoid dose may also impact on mineralocorticoid replacement as cortisol also binds the MR; 40 mg of hydrocortisone is equivalent to 100 µg of fludrocortisone. It is important to note that prednisone and prednisolone have reduced mineralocorticoid activity and dexamethasone has none. In patients living or traveling in areas with hot or tropical weather conditions, the fludrocortisone dose should be increased by 50–100 µg during the summer. Mineralocorticoid dose may also need to be adjusted during pregnancy due to the anti-mineralocorticoid activity of progesterone, but this is less often required than hydrocortisone dose adjustment. Plasma renin cannot serve as a monitoring tool during pregnancy because renin rises physiologically during gestation.

Adrenal androgen replacement is an option in patients with lack of energy, despite optimized glucocorticoid and mineralocorticoid replacement. It may also be indicated in women with features of androgen deficiency, including loss of libido. Adrenal androgen replacement can be achieved by once-daily administration of 25–50 mg DHEA. Treatment is monitored by measurement of DHEAS, androstenedione, testosterone, and sex hormone–binding globulin (SHBG) 24 h after the last DHEA dose.

GLUCOCORTICOID-INDUCED ADRENAL INSUFFICIENCY

A possible unwanted effect of glucocorticoid treatment is suppression of the hypothalamic-pituitary-adrenal axis. Glucocorticoid-induced adrenal insufficiency (GI-AI) can be observed with any route of

exogenous administration, including oral, topical, inhaled, intranasal, and intraarticular. Factors affecting the risk of GI-AI include the duration of glucocorticoid therapy, mode of administration, glucocorticoid dose and potency, concomitant drugs that interfere with glucocorticoid metabolism, and individual susceptibility. Up to half of long-term oral glucocorticoid users (0.5–1.8% of the general population in Western countries) develop GI-AI: patients treated with supraphysiologic doses for longer than 3–4 weeks carry the highest risk, whereas short-term therapy is generally safe. GI-AI has been described in around 8% of inhaled glucocorticoid users, but the risk increases substantially (21–27%) when high doses are used and for treatment duration >1 year. GI-AI has also been reported in approximately half of patients receiving intra-articular steroid injections, but evidence in this population is very limited. The use of multiple glucocorticoid formulations at the same time and the concomitant administration of strong cytochrome P450 3A4 inhibitors, which include several antibiotics, antifungals, and the protease inhibitor ritonavir, are among the factors dramatically increasing the risk of developing GI-AI. Ritonavir is the most reported offending medication, used as part of antiviral combinations to treat HIV infection, hepatitis C infection, and COVID-19. Other drugs that can increase the risk are opioids, which can also blunt the HPA axis response.

Clinicians who prescribe glucocorticoids should educate patients about the different aspects of glucocorticoid therapy, including the risk of GI-AI. If glucocorticoids are no longer required for the control of the underlying disease and the treatment duration is <3–4 weeks, glucocorticoids can be stopped abruptly. Conversely, patients on long-term treatment should be tapered down gradually until approaching a physiologic dose (e.g., 3–5 mg of prednisone). Patients who have developed a dependence on supraphysiologic glucocorticoid doses can develop withdrawal symptoms during tapering including malaise, fatigue, nausea, muscle and joint pain, and sleep and mood disturbances. Symptoms can be severe, and patients can sometimes benefit from a temporary increase in their glucocorticoid dose and a subsequent slower taper. Once a physiologic glucocorticoid dose has been achieved, patients should be tested for HPA axis recovery through an early-morning serum cortisol measurement, which provides information on the likelihood of GI-AI. There are no established cortisol cutoffs, which are influenced by the assay used and other factors including concurrent major stress and altered CBG levels leading to falsely elevated (e.g., oral estrogens, pregnancy) or falsely reduced (e.g., advanced liver cirrhosis, nephrotic syndrome) cortisol levels. Current international guidelines suggest that an early-morning cortisol <150 nmol/L (or 5 μg/dL) is highly suggestive of GI-AI, whereas values >300 nmol/L (or 10 μg/dL) are in keeping with HPA axis recovery. For indeterminate values, cosyntropin stimulation may be considered. Several clinicians do not routinely measure cortisol levels in patients tapering glucocorticoids; in such cases, patients must be educated and closely monitored for clinical manifestations of adrenal insufficiency, and biochemical testing should be swiftly arranged if there are any clinical concerns.

Patients with established GI-AI must be treated as any other patient with secondary adrenal insufficiency. Other than daily glucocorticoid replacement, patients should receive stress dose coverage when they are exposed to stress to avoid acute adrenal insufficiency. Mineralocorticoid therapy is not required due to preserved aldosterone production.

CONGENITAL ADRENAL HYPERPLASIA

(See also Chap. 402) CAH is caused by mutations in genes encoding steroidogenic enzymes involved in glucocorticoid synthesis (*CYP21A2, CYP17A1, HSD3B2, CYP11B1*) or in the cofactor enzyme P450 oxidoreductase that serves as an electron donor to CYP21A2 and CYP17A1 (Fig. 398-1). Invariably, patients affected by CAH exhibit glucocorticoid deficiency. Depending on the exact step of enzymatic block, they may also have excess production of mineralocorticoids or deficient production of sex steroids **(Table 398-10)**. The diagnosis of CAH is readily established by measurement of the steroids accumulating before the distinct enzymatic block, either in serum or in urine, preferably by the use of mass spectrometry–based assays (Table 398-10).

Mutations in *CYP21A2* are the most prevalent cause of CAH, responsible for 90–95% of cases. 21-Hydroxylase deficiency disrupts glucocorticoid and mineralocorticoid synthesis (Fig. 398-1), resulting in diminished negative feedback via the HPA axis. This leads to increased pituitary ACTH release, which drives increased synthesis of adrenal androgen precursors and subsequent androgen excess. The degree of impairment of glucocorticoid and mineralocorticoid secretion depends on the severity of mutations. Major loss-of-function mutations result in combined glucocorticoid and mineralocorticoid deficiency (classic CAH, neonatal presentation), whereas less severe mutations affect glucocorticoid synthesis only (simple virilizing CAH, neonatal or early childhood presentation). The mildest mutations result in the least severe clinical phenotype, nonclassic CAH, usually presenting during adolescence and early adulthood and with preserved glucocorticoid production.

Androgen excess is present in all patients and manifests with broad phenotypic variability, ranging from severe virilization of the external genitalia in neonatal girls (e.g., 46,XX disordered sex development [DSD]) to hirsutism and oligomenorrhea resembling a polycystic ovary syndrome phenotype in young women with nonclassic CAH. In countries without neonatal screening for CAH, boys with classic CAH usually present with life-threatening adrenal crisis in the first few weeks of life (salt-wasting crisis); a simple-virilizing genotype manifests with precocious pseudo-puberty and advanced bone age in early childhood, whereas men with nonclassic CAH are usually detected only through family screening.

Glucocorticoid treatment is more complex than for other causes of primary adrenal insufficiency as it not only needed to replace missing glucocorticoids but also to control the increased ACTH drive and subsequent androgen excess. Current treatment is hampered by the lack of glucocorticoid preparations that mimic the diurnal cortisol secretion profile, resulting in a prolonged period of ACTH stimulation and subsequent androgen production during the early morning hours. In childhood, optimization of growth and pubertal development are important goals of glucocorticoid treatment, in addition to prevention of adrenal crisis and treatment of 46,XX DSD. In adults, the focus shifts

TABLE 398-10 Variants of Congenital Adrenal Hyperplasia

VARIANT	GENE	IMPACT ON STEROID SYNTHESIS	DIAGNOSTIC MARKER STEROIDS IN SERUM (AND URINE)
21-Hydroxylase deficiency (21OHD)	*CYP21A2*	Glucocorticoid deficiency, mineralocorticoid deficiency, adrenal androgen excess	17-Hydroxyprogesterone, 21-deoxycortisol (pregnanetriol, 17-hydroxypregnanolone, pregnanetriolone)
11β-Hydroxylase deficiency (11OHD)	*CYP11B1*	Glucocorticoid deficiency, mineralocorticoid excess, adrenal androgen excess	11-deoxycortisol, 11-deoxycorticosterone (tetrahydro-11-deoxycortisol, tetrahydro-11-deoxycorticosterone)
17α-Hydroxylase deficiency (17OHD)	*CYP17A1*	(Glucocorticoid deficiency), mineralocorticoid excess, androgen deficiency	11-Deoxycorticosterone, corticosterone, pregnenolone, progesterone (tetrahydro-11-deoxycorticosterone, tetrahydrocorticosterone, pregnenediol, pregnanediol)
3β-Hydroxysteroid dehydrogenase deficiency (3bHSDD)	*HSD3B2*	Glucocorticoid deficiency, (mineralocorticoid deficiency), adrenal androgen excess (females and males), gonadal androgen deficiency (males)	17-Hydroxypregnanolone (pregnanetriol)
P450 oxidoreductase deficiency (PORD)	*POR*	Glucocorticoid deficiency, (mineralocorticoid excess), prenatal androgen excess and postnatal androgen deficiency, skeletal malformations	Pregnenolone, progesterone, 17-hydroxyprogesterone (pregnanediol, pregnanetriol)

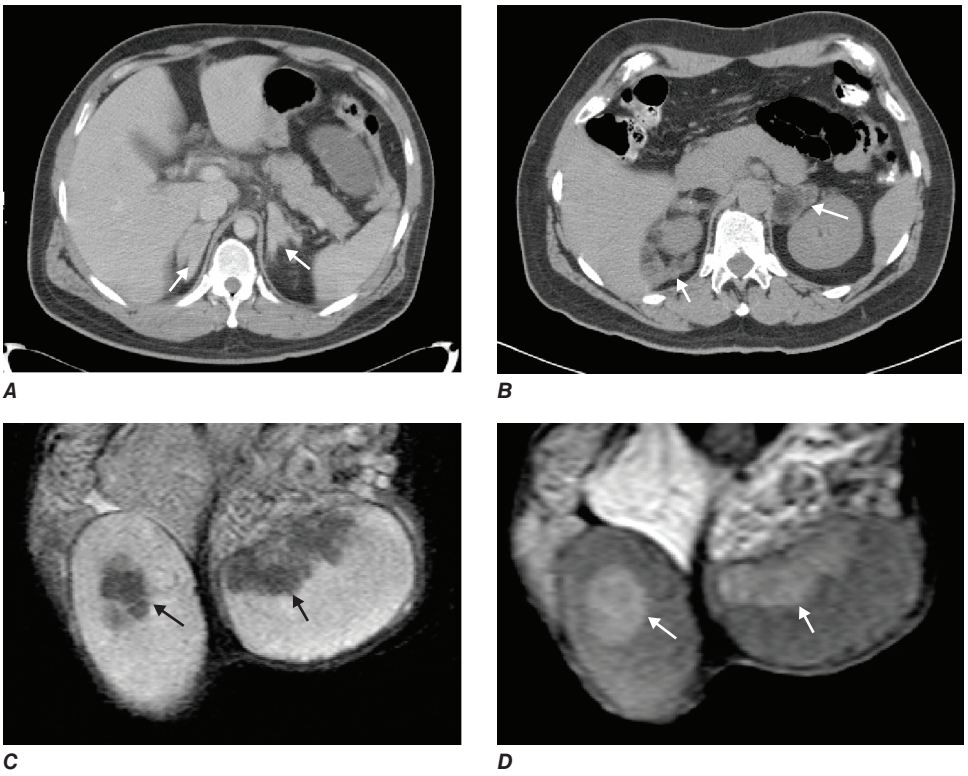

FIGURE 398-17 Imaging in congenital adrenal hyperplasia (CAH). Adrenal computed tomography scans showing homogenous bilateral hyperplasia in a young patient with classic CAH (***A***) and macronodular bilateral hyperplasia (***B***) in a middle-aged patient with classic CAH with longstanding poor disease control. Magnetic resonance imaging scan with T1-weighted (***C***) and T2-weighted (***D***) images showing bilateral testicular adrenal rest tumors (*arrows*) in a young patient with salt-wasting CAH. *(Used with permission from N. Reisch.)*

to preserving fertility and preventing side effects of glucocorticoid overtreatment, namely, the metabolic syndrome and osteoporosis. Fertility can be compromised in women due to oligomenorrhea/amenorrhea with chronic anovulation as a consequence of androgen excess. Men may develop testicular adrenal rest tissue (TART) **(Fig. 398-17)** consisting of hyperplastic cells with shared adrenal and gonadal characteristics located in the rete testis, which should not be confused with testicular tumors. TART can compromise sperm production and induce testicular fibrosis that may be irreversible.

TREATMENT

Congenital Adrenal Hyperplasia

Hydrocortisone is a good treatment option for the prevention of adrenal crisis, but longer acting prednisolone may be needed to control androgen excess. In children, hydrocortisone is given in divided doses at 1–1.5 times the normal cortisol production rate (~10–13 mg/m^2 per day). In adults, if hydrocortisone does not suffice, intermediate-acting glucocorticoids (e.g., prednisone) may be given, using the lowest dose necessary to suppress excess androgen production. For achieving fertility, dexamethasone treatment may be required but should only be given for the shortest possible time period to limit adverse metabolic side effects. The recent introduction of modified and delayed-release hydrocortisone, which mimics the endogenous physiologic cortisol release pattern, is promising, providing effective control of steroid precursor excess while the daily hydrocortisone dose is lower than required for immediate-release hydrocortisone. An oral corticotropin-releasing factor antagonist, Crinecerfont, has shown efficacy to reduce glucocorticoid replacement doses needed to suppress adrenal androgens.

Biochemical monitoring should include androstenedione and testosterone, aiming for the normal sex-specific reference range. 17OHP is a useful marker of overtreatment, indicated by 17OHP levels within the normal range of healthy controls. Glucocorticoid overtreatment may suppress the hypothalamic-pituitary-gonadal axis. Thus, treatment needs to be carefully titrated against clinical features of disease control. Stress-dose glucocorticoids should be given at double or triple the daily dose for surgery, acute illness, or severe trauma. Poorly controlled CAH can result in adrenocortical hyperplasia, which gave the disease its name, and may present as macronodular hyperplasia subsequent to long-standing ACTH excess (Fig. 398-17). The nodular areas can develop autonomous adrenal androgen production and may be unresponsive to glucocorticoid treatment. The prevalence of adrenomyelolipomas is increased in CAH; these are benign but can require surgical intervention due to lack of self-limiting growth.

Mineralocorticoid requirements change during life and are higher in children, explained by relative mineralocorticoid resistance that diminishes with ongoing maturation of the kidney. Children with CAH usually receive mineralocorticoid and salt replacement. However, young adults with CAH should undergo reassessment of their mineralocorticoid reserve. Plasma renin should be regularly monitored and kept within the upper half of the normal reference range.

FURTHER READING

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