TABLE 406-8 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)
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.

Diagnosis The diagnosis of adrenal insufficiency is established by the short cosyntropin test, a safe and reliable tool with excellent predictive diagnostic value **(Fig. 406-16)**. The cut-off for failure is usually defined at cortisol levels of <500–550 nmol/L (18–20 μg/dL) sampled 30–60 min after ACTH stimulation; the exact cut-off is dependent on the locally available assay. 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. 406-3). 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.

TABLE 406-9 SIGNS AND SYMPTOMS OF ADRENAL INSUFFICIENCY

Signs and Symptoms Caused by Glucocorticoid Deficiency
TB>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.

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. 406-16). 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.

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 100–200 mg hydrocortisone over 24 h, either by continuous infusion or 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 mineralocorticoid receptors.

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