CHAPTER 126

Thyroid and Adrenal Disorders

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Hyperthyroidism, hypothyroidism, and adrenal insufficiency are endocrine disorders that often manifest with chronic, nonspecific symptoms such as fatigue, weakness, and depression, and as a result are difficult to recognize in a typical medical encounter. With increased severity, each disorder has classic clinical manifestations that are more easily recognizable. Most importantly for the emergency physician, acute stresses can precipitate life-threatening illnesses in these patients, requiring vigorous medical management based on clinical judgment and suggestive laboratory data alone.

HYPERTHYROIDISM

Perspective

Background and Epidemiology

Although the terms *hyperthyroidism* and *thyrotoxicosis* are often used interchangeably, hyperthyroidism refers to conditions in which the production of thyroid hormone is increased, whereas thyrotoxicosis is defined as any state in which thyroid hormone levels are increased in the blood, whether it be from overproduction (Graves' disease, toxic multinodular goiter [TMG]), thyroid hormone release from an injured gland (thyroiditis), or exogenous thyroid hormone. The clinical spectrum of hyperthyroidism is a continuum from asymptomatic or subclinical disease to life-threatening thyroid storm.

On large random population screenings, the prevalence of hyperthyroidism is 0.5 to 2.2%, with more than half of these patients considered subclinical (prehyperthyroid state with depressed thyroid-stimulating hormone [TSH] and normal tetraiodothyronine, thyroxine [T_4]).[1-3] The prevalence of hyperthyroidism in women is tenfold greater than in men.

Graves' disease is the predominant cause of thyrotoxicosis, with TMG becoming more common with increasing age, exceeding Graves' disease by 2 to 1 in patients older than 55 years.[4,5] Hyperthyroidism is rare in childhood, but when seen is related to Graves' disease. It is estimated that 1 to 2% of patients with thyrotoxicosis will progress on to thyroid storm when an acute intercurrent stress supervenes.[6]

Principles of Disease

The follicular cells of the thyroid gland produce T_4 and triiodothyronine (T_3), which are regulated by a feedback loop with the anterior pituitary gland, which produces TSH. If levels of T_4 drop, TSH production is stimulated, whereas if the T_4 level is high, TSH is suppressed. TSH is in turn regulated by the hypothalamus's production of thyrotropin-releasing hormone (TRH).

Thyroid hormone synthesis by the follicular cells starts with the production of thyroglobulin, a large hormonal precursor protein with numerous tyrosines in its structure. Iodine is then actively transported into follicular cells where it is oxidized and then bound to tyrosine residues. Linking of iodotyrosines within thyroglobulin produces T_4 and T_3, which are released into the circulation by proteolyisis. All of T_4 is produced in the thyroid gland, whereas only 15 to 20% of T_3 is synthesized directly; the remainder is formed by deiodonation of T_4 in peripheral tissues. During systemic illness, deiodonation occurs, but at an inner ring of T_4, rather than the outer ring, and reverse T_3 is produced. T_4 is a prohormone with only mild intrinsic activity, whereas T_3 is the biologically active hormone, and reverse T_3 is inactive. Over 99.5% of thyroid hormones are protein-bound in the serum to thyronine-binding globulin (TBG) and other proteins, rendering them metabolically inactive. As a result, only free T_4 and free T_3 are clinically relevant.[4,6,7]

Although iodide is a substrate for thyroid hormone production, excess iodide inhibits iodide trapping and thyroglobulin iodination (the Wolff-Chaikoff effect) and most importantly blocks the release of thyroid hormone from the gland. Iodide's inhibition of thyroid hormone production and release is transient, with the gland escaping inhibition after 10 to 14 days. In contrast, an iodide load can induce hyperthyroidism (Jod-Basedow effect) in some patients with multinodular goiter and latent Graves' disease, especially if the patient is iodine-deficient to begin with.[4,6,7]

Thyroid hormone has effects on the metabolism of all tissues, exerting these at several levels. Thyroid hormone regulates gene activity by interaction at nuclear receptors. It has direct effects on metabolism by interaction with cellular enzymes, like adenosine triphosphatase. Most importantly, T_3 and T_4 increase the number and sensitivity of beta-adrenergic receptors, dramatically increasing response to endogenous catecholamines.[4,6]

Graves' disease is the most common cause of thyrotoxicosis and consists of the syndrome of hyperthyroidism, a diffuse symmetrical goiter, ophthalmopathy, and dermopathy. Graves' disease primarily affects females between the ages of 20 and 40 years, often those with a family history of thyroid disease. It is an autoimmune disorder in which B lymphocytes produce

immunoglobulins that stimulate the TSH receptor (thyroid-stimulating immunoglobulin [TSI]). The eye disease that accompanies the disease is thought to result from thyroid antibodies sensitized to common antigens in orbital fibroblasts and muscle.[4,6]

TMG is the second leading cause of hyperthyroidism, characterized by multiple autonomously functioning nodules typically developing in women older than 50 years of age. It is unusual in youth unless the patient has a preexisting nontoxic multinodular goiter or lives in a region of iodine deficiency. The population of the United States is generally iodine-sufficient, but areas of the world with populations that are deficient include Central America, South America, the Himalayas, Eastern Europe, and Central Africa. The hyperthyroidism in TMG is milder than Graves' disease and is gradual in onset, but acute presentations can occur when iodine replacement is given to an iodine-deficient individual. Because of the age of the patients, cardiovascular manifestations like atrial fibrillation and heart failure predominate,[8] whereas tremors and hypermetabolic features are less pronounced than Graves' disease. Muscle wasting and weakness is common, and the patient is often described as apathetic.[5] As multinodular goiters often extend retrosternally, obstructive symptoms may occur.[9,10]

A single hyperfunctioning (hot) nodule referred to as a toxic adenoma may occur in this same population, but it is less common than the multinodular form.

In thyroiditis, acute thyrotoxicosis can result from thyroid gland inflammation and cell breakdown with release of preformed thyroid hormone. Thyroiditis may be autoimmune in origin, infectious, or drug-induced. Hashimoto's thyrioditis is the most common type of thyroiditis. It is an autoimmune disorder characterized by thyroid antibodies and lymphocytic infiltration of the thyroid gland. Patients present with painless goiter and hypothyroidism, but thyrotoxicosis is rarely evident early in the disease (hashitoxicosis).[11]

Related autoimmune disorders of the thyroid include postpartum thyroiditis and sporadic thyroiditis. They are also referred to as painless, or silent, thyroiditis due to their small nontender goiter and mild symptoms. Five to 10% of pregnant women develop transient thyrotoxicosis 1 to 6 months postpartum, followed by a hypothyroid state for up to 6 months, then a return to baseline. There is a 70% chance of recurrence in subsequent pregnancies, and some women develop permanent hypothyroidism. Sporadic thyroiditis, which may account for up to 1% of thyrotoxicosis, is a similar entity, except for its lack of association with pregnancy.[12]

Subacute thyroiditis (de Quervain's thyroiditis) appears to be a viral or postviral disease that presents with a prodrome of fatigue, myalgias, and pharyngitis, followed by fever and severe anterior neck pain. Pain often radiates to the jaw and ears, and the gland is exquisitely tender. Symptoms of hyperthyroidism with sweats, palpitations, and tremor develop during this acute painful phase and may last several weeks, transitioning to a hypothyroid state for several months, then a return to a euthyroid state. Subacute thyroiditis may account for 2% of thyrotoxic patients and as is the case for other thyroid diseases, women predominate.[13]

Suppurative thyroiditis is a rare disorder that also presents with fever and anterior neck pain, but is marked by neck swelling, induration, and erythema and the presence of dysphonia and dysphagia. The cause is usually bacterial infection with abscess formation, but parasites, mycobacteria, and fungi may be responsible. Most patients have preexisting thyroid disease and are immunocompromised (AIDS).[14]

In North America, about 2% of patients treated with amiodarone develop thyrotoxicosis (higher in areas of iodine deficiency). Most of these cases result from a destructive thyroiditis, but a minority are due to amiodarone's iodine load (400 times the daily requirement), which may unmask hyperthyroidism in patients with multinodular goiter and subclinical Graves' disease. An exacerbation of the tachyarrhythmia that the patient is being treated for or heart failure is the typical presentation of a patient with thyrotoxicosis related to amiodarone. Other drugs that may induce thyroiditis include interferon, interleukin-2, granulocyte-macrophage colony-stimulating factor, and lithium.[12,15,16]

Chronic excess ingestion of thyroid hormone can result in thyrotoxicosis, referred to as thyrotoxicosis factitia. Although iatrogenic or patient errors may be responsible, medical personnel with psychiatric disease account for the majority of reported cases. Inadvertent ingestion of thyroid hormone in herbal products for weight reduction or in contaminated ground beef has been reported as well. Surprisingly, acute ingestions of thyroid hormone usually manifest only minor toxicity. The reasons for this are multiple: the 7-day half-life of T_4, the suppression of T_4-to-T_3 conversion and inhibition of endogenous hormone production by negative feedback loops, and the down-regulation of thyroid hormone receptors.[17,18]

A variety of rare forms of thyrotoxicosis have been described, including struma ovarii, thyroid carcinoma, hydatidiform mole, choriocarcinoma, and TSH-secreting pituitary adenomas[4,6,19] (Box 126-1).

Clinical Features

The symptoms and signs of thyrotoxicosis are caused by a hypermetabolic state and increased beta-adrenergic activity. Clinical manifestations vary from minimal (apathetic hyperthyroidism) to life-threatening (thyroid storm) and depend on the patient's age, duration of disease, the level and rate of rise of hormone levels, drug interactions, and the stress of intercurrent illness. Hyperadrenergic manifestations are often masked in the elderly. Thyrotoxicosis of long duration and gradual course may go unnoticed by many patients, or symptoms may be attributed to other causes like emotional stress, dieting, or physical deconditioning.[4,6]

BOX 126-1 CAUSES OF THYROTOXICOSIS

- Graves' disease (toxic diffuse goiter)
- Toxic multinodular goiter
- Toxic adenoma (single hot nodule)
- Factitious thyrotoxicosis
- Thyrotoxicosis associated with thyroiditis
  - Hashimoto's thyroiditis
  - Subacute (de Quervain's) thyroiditis
  - Postpartum thyroiditis
  - Sporadic thyroiditis
  - Amiodarone thyroiditis
- Iodine-induced hyperthyroidism (areas of iodine deficiency)
  - Amiodarone
  - Radiocontrast media
- Metastatic follicular thyroid carcinoma
- hCG-mediated thyrotoxicosis
  - Hydatidiform mole
  - Metastatic choriocarcinoma
  - Hyperemesis gravidarum
- TSH-producing pituitary tumors
- Struma ovarii

hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone.

Constitutional symptoms such as fatigue and generalized weakness are very common in thyrotoxicosis. Despite increased calorie intake, weight loss is seen in most patients, averaging about a 15% drop from baseline. To confound things, elderly patients often have a decreased appetite, leading to a suggestion of occult cancer. Hypermetabolic symptoms like heat intolerance, excessive sweating, and preference for the cold are most pronounced in younger patients.[20]

Neuropsychiatric complaints include anxiety, restlessness, tremor, feeling jittery or unable to sit still, insomnia, memory loss, and poor attention span. Family members often report emotional lability and agitation, which may progress to altered mental status and coma in thyroid storm. Weakness and fatigue of proximal muscle groups may result from thyroid myopathy, with patients often complaining of difficulty combing their hair, climbing stairs, or rising from a chair.[21] A sudden and profound muscle weakness progressing to flaccid paralysis is described in a thyrotoxic variant of hypokalemic periodic paralysis.[22]

Cardiopulmonary symptoms are very common and include palpitations, dyspnea on exertion, and reduced exercise tolerance. Older patients may present with new-onset angina, atrial fibrillation, or congestive heart failure as the presenting and only symptoms of thyroid disease.[8,16,23]

Gastrointestinal complaints often include more frequent bowel movements, but not diarrhea. Dysphagia may result from enlargement of the thyroid gland in Graves' disease or retrosternal extension of the gland in TMG. Nausea and vomiting may be seen with severe thyrotoxicosis.[4,6,9]

Reproductive endocrine function can be affected. Women often complain of a change in their menses, anywhere from amenorrhea to menometrorrhagia, and infertility is very common. Men may complain of a decrease in libido and breast swelling.[4,6]

Ocular complaints may result from ophthalmopathy in Graves' disease, but not in other causes of thyrotoxicosis. A sense of irritation and excessive tearing are early symptoms, with diplopia, retrobulbar discomfort, blurring of vision, and foreign body sensation occurring late in the disease[24] (Box 126-2).

Physical examination of the thyrotoxic patient may reveal distinctive findings, especially in younger individuals. The patient often appears anxious and fidgety, with a fine tremor of the hands and tongue and lightly closed eyelids. The skin feels warm, smooth, and velvety, likened to a baby's skin, especially over the elbows. The face is rosy and blushes readily. The hands may reveal palmar erythema and the distal part of the nails may separate from the nail bed (onycholysis, or Plummer's nails). Scalp hair is fine and brittle, and diffuse alopecia may occur.[4,6] Specifically in Graves' disease, about 5% of patients develop marked thickening of the pretibial skin by mucopolysaccharide infiltration of the dermis (pretibial myxedema). These lesions are painless, raised nodules and plaques that become confluent over the pretibial area and dorsum of the feet. Hyperpigmentation and induration are present, but pitting is absent, and pretibial myxedema is always associated with Graves' eye disease.[25]

Tachycardia is seen in virtually all patients, and there is widening of the pulse pressure with bounding pulses. The apical impulse is prominent and the heart sounds are enhanced. A systolic flow murmur is usually present, and rarely a friction rublike sound along the left sternal border (Means-Lerman scratch) may also be heard. Atrial fibrillation can be seen at any age in hyperthyroidism, with an overall prevalence of 2%, but the frequency is age-dependant, rising to 15% in patients older than 70 years.[26] Even subclinical hyperthyroidism appears to increase the prevalence of atrial fibrillation threefold over that in the average population.[27]

The ventricular response in thyrotoxic atrial fibrillation may be unusually fast, and the patient may be resistant to attempts to slow the rate as well as to convert to sinus rhythm. The chronic tachycardia and high cardiac output state in hyperthyroidism may lead to dilated cardiomyopathy, especially in elders and those with atrial fibrillation, resulting in an S_3 gallop and basilar crackles.[8,16,23,28] Primary pulmonary hypertension, sometimes associated with tricuspid regurgitation and right heart failure, may also be seen.[16,29,30]

The characteristic stare of thyrotoxicosis results from retraction of the upper and lower eyelids revealing a rim of sclera beyond the limbus. As the eyelids are sympathetically innervated, the increased sensitivity to adrenergic stimuli in thyrotoxicosis leads to the widening of the palpebral fissures. Other hyperadrenergic eye findings in thyrotoxic patients include lid lag and globe lag. In lid lag, the upper lid lags behind the globe when the patient is asked to look slowly downward. In globe lag, the globe lags behind the upper lid with slow upward gaze.[4,24]

Although stare is frequent in any form of thyrotoxicosis, proptosis of the globe is unique to Graves' disease, resulting from mucopolysaccharide infiltration and inflammation of the ocular muscles and soft tissue leading to exophthalmos. Imaging with ultrasound, computed tomography, or magnetic resonance imaging reveals orbital swelling in virtually all patients with Graves' disease, but only about 50% have clinical findings. Conjunctival injection, periorbital edema, and chemosis are early findings. Proptosis is defined by the anteroposterior distance from the lateral orbital ridge to the anterior cornea as greater than 20 mm. Progressive orbital involvement may lead to infiltration of the inferior rectus muscle with limitation of upward gaze. Very late findings can include keratitis from inability to close the eyes completely, and visual loss from optic nerve compression.[24] Treatment of hyperthyroidism, especially with radioactive iodine, may paradoxically aggravate Graves' eye disease.[31]

Chronic proximal muscle wasting and weakness may result from thyrotoxic myopathy.[21] More acute weakness with flaccidity may occur in Asian and Latino males from the thyrotoxic form of hypokalemic periodic paralysis.[22]

Most thyrotoxic patients have a palpable abnormality on examination of the thyroid gland. In Graves' disease, the gland is often two to three times normal size, but may be massively enlarged. A normal-size gland is unusual in younger patients, but more than 20% of older patients lack a goiter.[4] The thyroid

BOX 126-2 PATIENT COMPLAINTS IN THYROTOXICOSIS

Constitutional: Weight loss despite hyperphagia, fatigue, generalized weakness
Hypermetabolic: Heat intolerance, cold preference, excessive perspiration
Cardiorespiratory: Heart pounding and racing, dyspnea on exertion, chest pains
Psychiatric: Anxiety, restlessness, hyperkinesis, emotional lability, confusion
Muscular: Tremor, difficulty getting out of a chair or combing hair
Ophthalmologic: Tearing, irritation, wind sensitivity, diplopia, foreign body sensation
Thyroid Gland: Neck fullness, dysphagia, dysphonia
Dermatologic: Flushed feeling, hair loss, pretibial swelling
Reproductive: Oligomenorrhea, decreased libido, gynecomastia

gland in Graves' disease is symmetrical, smooth, soft to rubbery consistency, and has no evident nodules. In severe disease a palpable thrill and audible bruit are present and are usually continuous, rather than the systolic bruit seen with vascular disease. In TMG, the gland is variably enlarged and although multiple irregular nodules are often palpable, a single dominant nodule is not unusual, making distinguishing TMG from toxic adenoma difficult. The multinodular goiter may extend retrosternally, hiding it on examination unless the supraclavicular area is palpated on swallowing. By mass effect, a multinodular goiter may cause tracheal deviation and hoarseness as well as facial and neck vein engorgement, the latter becoming evident when the arms are elevated above the head (Pemberton's sign)[9,10] (Box 126-3).

In subacute thyroiditis, the thyroid gland is exquisitely tender, but redness or warmth of the overlying skin is only seen in suppurative thyroiditis. In the more typical entities of sporadic, postpartum, and Hashimoto's thyroiditis, the gland is nontender with modest to no enlargement.[11-14] In factitious thyrotoxicosis, the gland may be atrophic but this may be difficult to appreciate.

Thyroid Storm

Thyroid storm is a life-threatening decompensation of poorly controlled, untreated, or unrecognized thyrotoxicosis. It occurs in 1 to 2% of thyrotoxic patients and in about 10% of patients hospitalized for hyperthyroidism. Thyroid storm occurs predominately in Graves' disease, but occasionally is seen in TMG and toxic adenoma.[32,33] Occurrences in thyroiditis,[34] factitious thyrotoxicosis,[35] struma ovarii, hydatidiform mole,[19] and other causes of thyrotoxicosis are limited to rare case reports.

Thyroid storm is an exaggeration of the clinical manifestations of thyrotoxicosis, further distinguished by the presence of fever, marked tachycardia, central nervous system dysfunction, and gastrointestinal symptoms. Decompensation of one or more organ systems, such as shock or heart failure, also defines thyroid storm. If untreated, thyroid storm is uniformly fatal, and even with aggressive management it still carries a 20% mortality rate.[6,32,36,37]

BOX 126-3 PHYSICAL FINDINGS IN THYROTOXICOSIS

Vital Signs: Tachycardia, widened pulse pressure, bounding pulses, fever
Cardiac: Hyperdynamic precordium, systolic flow murmur, prominent heart sounds, systolic rub (Means-Lerman scratch), tricuspid regurgitation, atrial fibrillation, evidence of heart failure
Ophthalmologic: Widened palpebral fissures (stare), lid lag, globe lag, conjunctival injection, periorbital edema, proptosis, limitation of superior gaze
Neurologic: Fine tremor, hyper-reflexia, proximal muscle weakness
Psychiatric: Fidgety, emotionally labile, poor concentration
Dermatologic: Warm, moist, smooth skin; fine, brittle hair; alopecia, flushed facies; palmer erythema; hyperpigmented pretibial plaques, nodules, or induration that is nonpitting; onycholysis
Neck: Diffuse symmetrical thyroid enlargement, sometimes with a bruit and palpable thrill; thyroid with multiple irregular nodules or a prominent single nodule; tracheal deviation, venous prominence with arm elevation (Pemberton's sign)

Central to the pathophysiology of thyroid storm is an increase in catecholamine-binding sites and hence a heightened response to adrenergic stimuli. Superimposed on this vulnerable state is an acute stress that causes an outpouring of catecholamines that in conjunction with high levels of free T_4 and T_3 precipitates the exaggerated response we call thyroid storm.[4,6,37] It was once thought that thyroid storm resulted from a sudden dumping of thyroid hormone into the circulation, but except for sudden cessation of antithyroid therapy in a hyperthyroid patient and blunt or penetrating trauma to the thyroid gland (in both hyperthyroid and euthyroid patients) in which hormone leaks from injured acini, rapid rises in T_4 and T_3 are not responsible for storm.[38-41] In fact, hormone levels in thyroid storm are not generally distinguishable from poorly controlled thyrotoxicosis.[7]

Infection and sepsis are the most common precipitants of thyroid storm, but as fever is a prominent feature of storm, the thyrotoxic state may be overlooked. Historically, thyroid and nonthyroid surgery have been the leading triggers of thyroid storm, but identification and treatment of thyrotoxicosis preoperatively has dramatically decreased this as a precipitant. Other common precipitating events include myocardial infarction, stroke, pulmonary embolism, diabetic ketoacidosis, parturition, trauma, and administration of iodinated contrast media and amiodarone (Box 126-4).

The clinical presentation of thyroid storm is often dramatic. Although many of the findings of thyrotoxicosis are evident on

BOX 126-4 PRECIPITANTS OF THYROID STORM

Medical
Infection/sepsis
Cerebral vascular accident
Myocardial infarction
Congestive heart failure
Pulmonary embolism
Visceral infarction
Emotional stress
Acute manic crisis

Trauma
Thyroid surgery
Nonthyroid surgery
Blunt and penetrating trauma to the thyroid gland
Vigorous palpation of the thyroid gland
Burns

Endocrine
Hypoglycemia
Diabetic ketoacidosis
Hyperosmolar nonketotic coma

Drug-Related
Iodine-131 therapy
Premature withdrawal of antithyroid therapy
Ingestion of thyroid hormone
Iodinated contrast agents
Amiodarone therapy
Iodine ingestion
Anesthesia induction
Miscellaneous drugs (chemotherapy, pseudoephedrine, organophosphates, aspirin)

Pregnancy-Related
Toxemia of pregnancy
Hyperemesis gravidarum
Parturition and the immediate postpartum period

exam, certain features distinguish thyroid storm. Fever out of proportion to the physician's expectations is characteristic of storm, sometimes mimicking heatstroke with temperatures exceeding 106° F. Inappropriately excessive diaphoresis is frequently observed, and sinus tachycardia over 140 beats per minute is common.[4,6,36,37] Heart rates exceeding 150 beats per minute may be indicative of atrial fibrillation or other supraventricular tachycardias. In addition, symptoms and signs of congestive heart failure often accompany such rapid rates.[8,16]

Altered mental status from metabolic encephalopathy is a hallmark of thyroid storm, ranging from restlessness and agitation to delirium, seizures, and coma.[21,42]

Gastrointestinal symptoms are often pronounced, with nausea, vomiting, and diarrhea leading to volume depletion and hypotension. Abdominal pain mimicking bowel obstruction may be present. An unusual complication of severe thyrotoxicosis is cholestatic jaundice, which carries a bad prognosis if hepatic failure ensues.[43]

Although hyperthermia, exaggerated tachycardia, and altered mental status can quickly identify possible thyroid storm, the clinical presentation can be difficult to differentiate from uncomplicated thyrotoxicosis. Taking into account the severity of fever, tachycardia, central nervous system dysfunction, congestive heart failure, and gastrointestinal symptoms, Burch and Wartofsky developed a scoring system to help distinguish uncomplicated thyrotoxicosis from impending thyroid storm and true thyroid storm (Table 126-1). Although this scoring system has not been rigorously tested, it may prove useful in decisions to treat in borderline cases.[44]

Table 126-1 Diagnostic Criteria for Thyroid Storm

	SCORE
Fever (°F)	
99–99.9	5
100–100.9	10
101–101.9	15
102–102.9	20
103–103.9	25
≥104	30
Tachycardia (beats/min)	
90–109	5
110–119	10
120–129	15
130–139	20
≥140	25
Mental Status	
Normal	0
Mild agitation	10
Delirium, psychosis	
Extreme lethargy	20
Coma/seizures	30
Congestive Heart Failure	
Absent	0
Mild (edema)	5
Moderate (rales)	10
Pulmonary edema	15
Atrial fibrillation	10
Gastrointestinal and Hepatic Symptoms	
None	0
Nausea, vomiting	10
Diarrhea, abdominal pain	
Unexplained jaundice	20
Precipitating Event	
None	0
Present	10

Adapted from Burch HB, Wartofsky L: Life-threatening thyrotoxicosis: Thyroid storm. Endocrinol Metab Clin North Am 1993; 22: 263–277.

Tally the maximum score from each category. A score of 45 or greater suggests thyroid storm; a score of 25–44 suggests impending storm, and a score below 25 is unlikely to represent thyroid storm.

Diagnostic Strategies

The best screening tool for the diagnosis of thyrotoxicosis is the ultrasensitive TSH, which is depressed or undetectable in thyrotoxicosis. A normal TSH excludes hyperthyroidism and an elevated TSH is diagnostic for hypothyroidism, except in the rare circumstance of secondary hyperthyroidism from overproduction of TSH by a pituitary adenoma. Although a nondetectable TSH is specific for thyrotoxicosis, a modest depression of the TSH measurement is not always the result of mild or subclinical hyperthyroidism. Severe systemic illness may depress TSH production, leading to low levels of TSH, free T_3, and free T_4. This nonthyroidal illness pattern is often referred to as the euthyroid sick syndrome, and it appears to be a transient form of central hypothyroidism, an adaptive response to slow metabolism during systemic stress. Chronic conditions in which TSH may be suppressed include anorexia nervosa, depression, and renal failure. Medications, including dopamine, glucocorticoids, somatostatin, and octreotide, may also depress TSH levels.[6,7]

Although screening for thyroid disease with TSH is a reasonable strategy, measurement of thyroid hormone levels is required for a definitive diagnosis. Total T_3 and total T_4 assays may be misleading as they are influenced by changes in TBG. Increases in TBG with resultant false elevations in total T_3 and T_4 are seen in pregnancy, infectious hepatitis, and drug therapy with estrogens, tamoxifen, methadone, or heroin. In contrast, decreases in TBG with subsequent low total T_3 and T_4 are seen in cirrhosis, malnutrition, and nephrotic syndrome, as well as treatment with androgens or glucocorticoids. Lastly, many drugs inhibit the binding of T_3 and T_4 to TBG, thus resulting in higher levels of free T_3 and free T_4 levels, which will not be reflected in the total hormone measurements. Such drugs include salicylates, nonsteroidal anti-inflammatories, heparin, furosemide, diphenylhydantoin, carbamazepine, and sulfonylureas. Because of the many limitations in the measurement of total hormone levels, only free T_3 and free T_4 assays should be relied on.[6,7]

The combination of both free T_4 and free T_3 elevation with TSH suppression is diagnostic of thyrotoxicosis. If TSH is suppressed and free T_4 is normal, subclinical hyperthyroidism is likely; however, about 5% of patients with thyrotoxicosis have an elevated free T_3 and normal free T_4—referred to as T_3 toxicosis, an entity more common in TMG. The reverse situation, in which free T_3 is normal and free T_4 is elevated may be seen in thyroiditis, exogenous levothyroxine ingestion, and hyperthyroidism in the elderly, often with suppressed T_4 to T_3 conversion due to comorbid illness[4,7] (Table 126-2).

Differentiating Graves' disease from other forms of thyrotoxicosis is usually straightforward clinically, but the measurement of thyroid antibodies to thyroglobulin and thyroid peroxidase may be helpful in questionable cases.

In addition to thyroid function tests, multiple laboratory abnormalities may be seen in thyrotoxicosis and thyroid storm. Hyperglycemia is the most common abnormality, seen in up to half the patients, likely related to glycogenolysis and catecholamine-mediated antagonism of insulin. Mild hypercalcemia is seen in 10% of patients and is related to hormone-mediated bone resorption, osteoporosis, and increased fracture risk.

Table 126-2 Thyroid Function Test Interpretation

TSH	FREE T_4	FREE T_3	DISEASE
Normal	Normal	Normal	None
Low	High	High	Hyperthyroidism
Low	Normal	Normal	Subclinical hyperthyroidism
Low	Normal	High	T_3 toxicosis
Low	High	Normal	Thyroiditis, T_4 ingestion, hyperthyroidism in the elderly or with comorbid illness
Low	Low	Low	Euthyroid sick syndrome; central hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism; recovery from euthyroid sick syndrome
High	Low	Low	Primary hypothyroidism
High	High	High	TSH producing pituitary adenoma

T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone.

Abnormal liver function tests are frequent in hyperthyroidism. The abnormalities observed include mild increases in serum aspartate transaminase, alanine transaminase, lactate dehydrogenase, bilirubin, and, most commonly, alkaline phosphatase. Although elevated serum bilirubin occurs in hyperthyroidism, clinical jaundice develops infrequently. Other abnormalities may include a leukocytosis with a left shift, a mild normocytic normochromic anemia, and low serum cholesterol levels.[7]

The diagnostic evaluation for thyroiditis is more difficult. If there is exquisite gland tenderness and a sedimentation rate greater than 100, the diagnosis of subacute thyroiditis is likely. Other forms of thyroiditis, however, lack these findings.[12,13] Doppler ultrasound of the thyroid may be helpful in differentiating among the hypervascular enlarged gland of Graves' disease, the nodules of TMG, and thyroiditis or factitious thyrotoxicosis (decreased Doppler flow).[45] Another option is a radioactive iodine uptake, which is depressed in thyroiditis and factitious thyrotoxicosis but increased in hyperthyroidism. If exogenous thyroid hormone abuse is suggested, measurement of thyroglobulin levels may confirm the diagnosis, being very low in factitious thyrotoxicosis but elevated in all other forms of thyrotoxicosis.[35]

Differential Considerations

The overtly thyrotoxic patient is often thought to be very anxious, manic, or in the midst of a panic attack. In addition, hyperadreneric signs may suggest sympathomimetic (cocaine, amphetamine) or anticholinergic intoxication or a withdrawal syndrome (alcohol, narcotics, sedative-hypnotics). The high fever and altered mental status seen in thyroid storm may mimic heatstroke, neuroleptic malignant syndrome, serotonin syndrome, bacterial meningitis, and sepsis.

In elders, the hyperadrenergic features of thyrotoxicosis may be masked, facial muscles may lack expression, and mental status may be depressed leading to the syndrome of apathetic hyperthyroidism. Patients with multinodular goiters and those older than 70 are most likely to present in this manner. New-onset atrial fibrillation and congestive heart failure exacerbations are often the presenting symptoms of apathetic hyperthyroidism. In addition, elders with thyrotoxicosis may have significant weight loss without increased appetite, suggestive of occult cancer.

Management

Patients with mild thyrotoxicosis with minor symptoms can often await outpatient follow-up for initiation of treatment. Of more importance to the emergency physician is the avoidance of interventions that may increase thyroid hormone levels or accentuate adrenergic stimuli. Thyrotoxic patients should not receive iodinated contrast media or amiodarone, both of which present an iodine load that may enhance thyroid hormone production.[46] Caution is advised with the use of aspirin and nonsteroidal anti-inflammatories as they may interfere with protein binding of thyroid hormone, leading to increases in free T_4 and T_3.[47] Drugs such as pseudoephedrine, ketamine, and albuterol that increase sympathomimetic tone should also be used with caution.[48] Patients with thyrotoxicosis who are symptomatic may require initiation of beta-blocker therapy in the emergency department, but the initiation of thionamides like propylthiouracil (PTU) and methimazole are rarely indicated.

The prompt recognition and treatment of thyroid storm is crucial for patient survival. Therapeutic interventions have several aims: (1) reducing production of thyroid hormone, (2) inhibiting thyroid hormone release, (3) blocking peripheral conversion of T_4 to T_3, (4) initiating beta-adrenergic blockade, (5) instituting general supportive measures, and (6) identifying and treating the precipitating event.

Reducing Production of Thyroid Hormone

The first-line treatment of thyroid storm is the use of thionamides, which inhibit oxidation and organic binding of iodine to thyroglobulin, thus blocking synthesis of thyroid hormone. PTU and methimazole are available, but PTU is preferred due to its additional effect of impairing conversion of T_4 to T_3. PTU is given as an initial loading dose of 600 to 1000 mg by mouth, followed by 200 to 250 mg every 4 hours. The recommended dose for methimazole is 20 to 25 mg initially with the same dose repeated every 4 hours.[4,6,32,36,37] If a patient cannot take medication orally, the same dose can be given by nasogastric tube or by retention enema. Such solutions require pharmacy preparation on a case-by-case basis.[49] Due to solubility limitations, there is no IV form of PTU or methimazole, yet methimazole has been tried intravenously. Such solutions also require pharmacy preparation, and can be administered 30 mg every 6 hours.[50] The intravenous (IV) route should be considered only in a dire situation where oral or rectal administration is not feasible or ineffective (Box 126-5).

Inhibiting Thyroid Hormone Release

Although thyroid hormone synthesis can be stopped by thionamides, preformed hormone in the gland is still available for release. Inorganic iodine blocks the release of thyroid hormone stored in the gland, but administration should be delayed at least 1 hour after PTU or methimazole is started. The reason for this delay is that an iodine load presented to an actively synthesizing gland provides further substrate for hormone production and release. Iodine is given as saturated solution of potassium iodide (SSKI) 5 gtt every 6 hours or Lugol's solution 8 gtt every 6 hours. Published dosage recommendations range from one-half to double these doses, yet the effective iodine dose appears to be just a fraction of these numbers. As there is no apparent harm in administering larger iodine doses, this middle figure is most commonly recommended.[4,6,32,36,37] Because no IV form of iodide is available, the rectal route can be used if the oral or nasogastric route cannot be used.[49] If allergy to iodine is encountered, lithium is an alternative agent

BOX 126-5 MANAGEMENT OF THYROID STORM

Inhibition of Thyroid Hormone Synthesis

Propylthiouracil 600–1000 mg loading dose, then 200–250 mg every 4 hr
OR
Methimazole 20–25 mg initially, then 20–25 mg every 4 hr
(*Preferred route:* PO or NG. *Alternative route:* PR. Enema prepared by pharmacy. Same dose for all routes. No IV preparation is available, but IV methimazole can be prepared with the use of a Millipore filter and given 30 mg every 6 hr)

Inhibition of Thyroid Hormone Release

Saturated solution of potassium iodide (SSKI) 5 gtt by mouth, NG, or PR every 6 hr
OR
Lugol's solution 8 gtt by mouth, NG, or PR every 6 hr
OR
Sodium Iodide 500 mg in solution prepared by pharmacy IV every 12 hr
OR
If allergic to iodine, lithium carbonate 300 mg by mouth or NG every 6 hr

Beta-adrenergic Blockade

Propanolol 60–80 mg PO every 6 hr
OR
Metoprolol 50 mg PO every 6 to 12 hr
If IV route required, propanolol 0.5–1.0 mg IV slow push test dose, then repeat every 15 min to desired effect, then 2–3 mg every 3 hr
OR
Esmolol 250–500 µg/kg bolus, then 50–100 µg/kg/min infusion
Strict contraindication to beta-blocker: reserpine 0.5 mg PO every 6 hr

Administration of Corticosteroids (inhibit T_4 to T_3 conversion, treat relative adrenal insufficiency)

Hydrocortisone 300 mg IV, followed by 100 mg every 6 hr
OR
Dexamethasone 2–4 mg IV every 6 hr

Diagnosis and Treatment of Underlying Precipitant

Consider empirical antibiotics if critical

Supportive Measures

Volume resuscitation and replacement of glycogen stores
D_5/0.9NS 125–1000 mL/hr depending on volume status and CHF
Tylenol with caution
Cooling blanket, fans, ice packs, ice lavage

Miscellaneous

Lorazepam or diazepam as anxiolytic and to decrease central sympathetic outflow
L-Carnitine (block entry of thyroid hormone into cells), 1 g PO every 12 hr
Cholestyramine (block enterohepatic recirculation of thyroid hormone), 4 g PO every 6 hr

CHF, congestive heart failure; D_5/0.9NS, 5% dextrose in 0.9% normal saline; IV, intravenous; NG, nasogastric; PO, by mouth; PR, in rectum; T_3, triiodothyronine; T_4, thyroxine.

that impairs thyroid hormone release. The lithium dose is 300 mg every 6 hours by mouth or nasogastric tube, but lithium levels should be monitored to maintain a level of about 1 mg/L. Iodine should not be used in amiodarone-induced thyrotoxicosis as iodine overload may contribute to amiodarone's toxicity. In hyperthyroidism unmasked by iodine excess (iodinated contrast agents), lithium should be used to inhibit hormone release and further iodine administration avoided. Iodine's effects cease after 2 to 3 weeks of therapy, thus a delayed exacerbation of hyperthyroidism may ensue unless adequate thionamide therapy has been maintained.[51]

Blocking Peripheral Conversion of T_4 to T_3 and Initiating Beta-adrenergic Blockade

Blockade of peripheral hyperadrenergic activity by beta-blockers is a cornerstone of therapy in thyroid storm and symptomatic thyrotoxicosis. Propanolol has traditionally been the beta-blocker of choice because it blocks conversion of T_4 to T_3 and its nonselective effects also improve tremor, hyperpyrexia, and restlessness. Dosage recommendations vary from 20 to 120 mg by mouth at 6-hour intervals, with most authors suggesting 60 to 80 mg per dose.[4,6,32,36,37] If the patient cannot take anything by mouth or rapid beta-blockade is desired while waiting for the oral dose to be effective, IV propanolol can be administered as a test dose of 0.5 to 1 mg over 10 minutes. A cautious start is recommended if there is evidence of severe heart failure or hypotension as there are rare case reports of cardiovascular collapse after propanolol administration in thyroid storm.[52] If the patient tolerates the initial dose of propanolol, it can be repeated every 15 minutes until the desired effect is achieved, then transitioning to 3-hour intervals with 1 to 3 mg boluses. If there are contraindications or concerns about beta-blocker therapy, a short-acting agent such as esmolol may be prudent. Esmolol is usually started as a loading dose of 250 to 500 µg/kg, then continued as an infusion of 50 to 100 µg/kg/min.[53] $Beta_1$-selective drugs like esmolol or metoprolol (50 mg every 6–12 hours) may be preferable in asthma patients, but if not tolerated, reserpine 0.5 mg orally every 6 hours could be considered, while monitoring for hypotension.[54]

Corticosteroids are recommended in thyroid storm, because they inhibit peripheral conversion of T_4 to T_3, as well as block the release of hormone from the gland. The synergistic effect of PTU, iodide, and steroids in thyrotoxicosis can restore the concentration of T_3 to normal within 24 to 48 hours.[36] Corticosteroids are also suggested due to an absolute or relative adrenal insufficiency that can occur in thyroid storm. Addison's disease can occur concomitantly with Graves' disease in polyglandular autoimmune syndrome type 2, but more importantly, the increased clearance of cortisol in thyrotoxicosis coupled with the high demand for cortisol in such critically ill patients leads to a relative adrenal insufficiency in most. Hydrocortisone can be given as an initial bolus of 100 to 300 mg IV, followed by 100 mg every 8 hours for several days. Dexamethasone has also been used in this setting as well, in doses of 2 to 4 mg every 6 hours or 8 mg every 24 hours.[55]

Instituting General Supportive Measures

Supportive measures are equally important in the management of thyroid storm. Fluid resuscitation should be vigorous

BOX 126-6 THYROTOXICOSIS AND THYROID STORM: SPECIAL SITUATIONS

Congestive Heart Failure
If rate-related, high-output failure
- Beta-blockade is first-line therapy (dose as in Box 126-5)
- ACEI, digoxin, diuretics as needed

If depressed EF
- Avoid beta-blocker or ¼ dose
- ACEI if BP adequate
- Digoxin and furosemide as needed

If pulmonary hypertension
- Oxygen
- Sildenifil

Atrial Fibrillation
Beta-blocker preferred for rate control (doses as in Box 126-5)
Calcium channel blockers prone to hypotension; diltiazem
- 10-mg test dose. Avoid verapamil

Digoxin less effective but may be tried
Amiodarone should be avoided due to iodine load
Refractory to conversion to sinus unless euthyroid first

Thyroiditis (Subacute)
NSAIDs for inflammation and pain control
Prednisone 40 mg/day if refractory to NSAIDs
Beta-blockade to control thyrotoxic symptoms
No role for PTU, methimazole, or iodides

Factitious Thyrotoxicosis
Beta-blockade for thyrotoxic symptoms
Cholestyramine to block absorption of ingested thyroid hormone
No role for PTU, methimazole, or iodides

ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; EF, ejection fraction; NSAIDs, nonsteroidal anti-inflammatory drugs; PTU, propylthiouracil.

unless clear signs of congestive heart failure are evident. Due to the depletion of glycogen stores in thyrotoxicosis, a 5% dextrose solution is recommended; hence for volume replacement, D5/0.9NS is a rational choice. As high fever to the point of heatstroke is not unusual in thyroid storm, therapy to dissipate heat is a priority, typically by means of cool mists, fans, ice packs, cooling blankets, and ice water lavage. Acetaminophen could be used for moderate fever, but as hepatic dysfunction may occur in storm, it should be used with caution. Aspirin is contraindicated in thyroid storm because it increases levels of free thyroid hormone.[4,6,32,36,37]

Treatment to hasten elimination of thyroid hormone has been described. Cholestyramine, an anion exchange resin, binds thyroid hormone in the bowel lumen, thus interrupting enterohepatic recirculation. Cholestyramine in a dose of 4 g every 6 hours has been shown to result in a more rapid decline in hormone levels than thionamides alone.[56] Colestipol has been shown to have a similar effect, but not ezetimibe.[57] Progressive deterioration in a patient with thyroid storm, despite aggressive multidrug therapy, may lead to the consideration of plasmapharesis, plasma exchange, or dialysis to attempt rapid reduction in thyroid hormone levels.[58]

Benzodiazepines for agitation and hypomania of thyrotoxicosis may be considered as the hyperadrenergic state resembles cocaine intoxication. L-Carnitine has been described in thyroid storm, its suggested mechanism being the inhibition of thyroid hormone entry into cell nuclei. The dose used is 1 g every 12 hours by mouth[59] (Box 126-5).

Radioactive iodine or surgery has no role in the management of thyroid storm or thyrotoxicosis until a sustained euthyroid state has been achieved, as these interventions can precipitate storm themselves.[60]

Beta-blockers are a mainstay in the treatment of high-output heart failure as defined by a normal or exaggerated ejection fraction on echocardiography.[8,16] Preexisting heart disease aggravated by thyrotoxicosis may be associated with low-output congestive heart failure (low ejection fraction on echocardiography), in which circumstance caution should be exercised with the use of beta-blockers, because cases of cardiovascular collapse have been described with their use in this setting.[52] Routine management with angiotensin-converting enzyme inhibitors, diuretics, and digoxin are appropriate in both groups.[8,16]

The management of atrial fibrillation in thyrotoxicosis also has unique features. The rapid ventricular response generally requires high doses of beta-blocker for control. If thyroid storm is present, calcium channel blockers should be avoided as hypotension is a potential complication. Digoxin tends to be ineffective in this setting, but could be tried. Amiodarone should not be used due to its iodine load and potential to induce thyroiditis. Attempts to convert to sinus rhythm are usually fruitless while the patient remains thyrotoxic and thus should be postponed until the patient is euthyroid.[16,26]

Pain and tenderness as seen in subacute thyroiditis is treated with nonsteroidal anti-inflammatories. If refractory or recurrent, prednisone may be required.[12,13] Thyrotoxicosis in thyroiditis is usually mild, and beta-blockers alone are recommended. In fact, thionamides and iodine have no effect in thyroiditis. If drug-related, the offending agent (amiodarone, interferon) should be stopped immediately. Thyrotoxicosis from exogenous thyroid hormone ingestion should be treated with beta-blockade alone because the thyroid gland is shut down, thereby rendering thionamides and iodine ineffective. Cholestyramine could be used to bind hormone in the gut in both the acute and chronic intoxication, but evidence to its efficacy is limited[17,35] (Box 126-6).

Special mention should be made regarding potential toxicity of thionamide therapy, as it may be a presenting manifestation of a thyrotoxic patient. The minor adverse reactions that occur in up to 5% of patients include drug fever, alteration in sense of taste, skin eruptions, arthralgias, and sialoadentitis. Such reactions should not lead to discontinuation of therapy in the patient with thyroid storm, but should be reason to stop in the mildly thyrotoxic individual. The most feared and life-threatening adverse reaction to PTU and methimazole is agranulocytosis, which is often heralded by onset of fever and severe sore throat. Any patient who develops fever while on thionamide therapy should have his or her white blood cell count determined and if at all depressed, therapy should be stopped immediately. Fortunately, such reactions occur only in 3 or 4 patients per 1000. Other infrequent yet serious reactions to thionamides include hepatitis, vasculitis, and polyarthritis.[61]

Simultaneous with the previously detailed treatment measures, an aggressive search for an underlying precipitant of thyroid storm should be undertaken. As infection is the most common culprit, a chest radiograph, urinalysis, and blood cultures are routine. Silent myocardial ischemia should be assessed by an electrocardiogram and troponin, and the possibility of stroke or pulmonary embolism considered. Empirical use of antibiotics are tempting in the setting of thyroid storm, but restraint is prudent unless there is strong clinical evidence.

Aggressive management of thyroid storm with PTU followed by iodine, beta-blockers, corticosteroids, fluid resuscitation, rapid cooling, and treatment of the precipitating illness can resolve fever, tachycardia, and altered mental status within a 24-hour period. All patients with storm should be admitted to an intensive care setting, and any interruption in therapy should be avoided as it can lead to a sudden recrudescence of symptoms and death.

HYPOTHYROIDISM

Perspective

The clinical presentation of the hypothyroid patient can vary from asymptomatic or subclinical cases to life-threatening myxedema coma. In random population sampling, the prevalence of TSH elevation has ranged from 3.7 to 9.5%, with the majority of these having a normal free T_4, which by definition is subclinical hypothyroidism. Overt hypothyroidism (elevated TSH and depressed free T_4) is seen in a minority of these patients, about 0.3% of the population overall, with the prevalence rising with age, such that patients older than 80 years have a fivefold greater likelihood of developing hypothyroidism than do 12- to 49-year-olds.[1-3] Some surveys estimate the incidence of hypothyroidism as high as 20% in elders.[5] The female to male ratio is about 4:3 in hypothyroidism, in contrast to 8:1 for hyperthyroidism. Race differences are notable in that hypothyroidism is seen in 5.1% of whites, 4.1% of Hispanic-Americans, and 1.7% of African-Americans.[1-3]

Principles of Disease

The etiology of hypothyroidism includes primary thyroid failure, thyroiditis, pituitary/hypothalamic causes, drug-related and iatrogenic. The vast majority of hypothyroidism encountered in the United States is due to thyroid gland failure, and the majority of these are caused by autoimmune destruction of the gland in Hashimoto's thyroiditis. In younger patients, the disease is associated with a goiter and elevated titers of antithyroid antibodies, specifically to thyroid peroxidase, thyroglobulin, and TSH. The TSH receptor antibody in Hashimoto's disease blocks the receptor, in contrast to the stimulating antibody in Graves' disease. In older patients, the thyroid gland is typically atrophic, and evidence of autoimmunity is often lacking.[62-64]

End-stage Graves' disease can also result in autoimmune destruction of the thyroid gland, occurring spontaneously following several exacerbations of hyperthyroidism. More commonly, hypothyroidism follows treatment of Graves' disease with radioactive iodine or thyroidectomy.

Drug-induced hypothyroidism is often encountered with lithium carbonate because it inhibits hormone release. Iodine excess, as seen with amiodarone, iodinated contrast media, kelp supplements, and iodine-containing cough medicines, can impair thyroid hormone release and synthesis (Wolff-Chaikoff effect), thereby converting subclinical hypothyroidism to overt hypothyroidism and sometimes precipitating hypothyroidism de novo. In contrast, iodine-deficient patients administered an iodine load increase production of thyroid hormone and may develop hyperthyroidism. Interferon-alfa can result in hypothyroidism by precipitating Hashimoto's thyroiditis. Overtreatment with PTU or methimazole may lead to hypothyroidism due to their inhibition of hormone synthesis. Phenytoin, carbamazepine, phenobarbital, and rifampin may aggravate hypothyroidism by enhancing metabolism of thyroid hormone.[62-64]

Patients on thyroid replacement therapy can develop hypothyroidism when drugs are introduced that interfere with hormone absorption, including iron, calcium, phosphate binders, sucralfate, aluminum hydroxide, cholestyramine, colestipol, and even coffee.[65]

Iatrogenic causes of hypothyroidism include neck irradiation for cancer or lymphoma and thyroidectomy for nodular goiter or thyroid cancer.

Hypothyroidism may be seen as a late phase of thyroiditis.[12] In Hashimoto's disease the initial hyperthyroid phase is rarely identified, and hypothyroidism predominates.[11] In subacute, silent, and postpartum thyroiditis the hyperthyroid phase is usually clinically evident, and the hypothyroidism is often very mild and transient, but can become chronic.[13]

Rare causes of hypothyroidism include inherited disorders of hormone biosynthesis and central hypothyroidism. Central causes are usually due to pituitary destruction by an adenoma, hemorrhage (Sheehan's syndrome), or infiltration (sarcoid, amyloid), but can also result from hypothalamic dysfunction.[66]

A form of central hypothyroidism that appears to be an adaptive response to significant nonthyroidal illness is the euthyroid sick syndrome. Mild suppression of TSH release leads to a decrease in free T_4 and T_3. Impairment of T_4 to T_3 conversion also develops leading to elevation of reverse T_3 levels. Euthyroid sick syndrome remits spontaneously with resolution of the acute illness, and treatment with thyroid replacement is not indicated. Drugs that may contribute to TSH suppression in nonthyroidal illness include glucocorticoids, dopamine, and octreotide[62,64,67] (Box 126-7).

Clinical Features

Symptoms and signs of hypothyroidism are often very subtle and difficult to recognize in their milder presentation. Patients often ignore or tolerate symptoms when their development is very gradual, as is the case in Hashimoto's thyroiditis, where the delay from symptom appearance and diagnosis may be several years. Acute hypothyroidism presenting over weeks to months may be seen in thyroiditis or withdrawal of exogenous thyroid hormone. Chronic disease may present acutely due to drug toxicity or when an intercurrent illness is superimposed.[62-64]

The clinical manifestations of hypothyroidism result from changes induced by lack of thyroid hormone, most notably a generalized slowing of metabolic processes (due to altered gene expression and decreased catecholamine sensitivity) and an accumulation of glycosaminoglycans (decreased metabolism) in interstitial fluids.

Patients with hypothyroidism typically have pale, cool skin from decreased blood flow and fluid accumulation. Epidermal and sweat gland changes result in dry, scaly, rough skin. The skin is firm to the touch and appears swollen, but does not pit. In severe, chronic disease, the patient has a typical facies characterized by puffy eyelids, broad nose, swollen lips, and macroglossia. The hair in hypothyroidism becomes coarse and brittle, and alopecia is common. Thinning of the lateral third

BOX 126-7 CAUSES OF HYPOTHYROIDISM

Primary Hypothyroidism

Autoimmune hypothyroidism
- Hashimoto's thyroiditis (chronic—atrophic thyroid, acute with goiter)
- Graves' disease (end stage)

Iatrogenic
- Radioactive iodine therapy for Graves' disease
- Thyroidectomy for Graves' disease, nodular goiter, or thyroid cancer
- External neck irradiation for lymphoma or head and neck cancer

Iodine-related
- Iodine deficiency (common worldwide, but rare in North America)
- Iodine excess (inhibition of hormone release can unmask autoimmune thyroid disease) (see under Drug-related)

Drug-related
- Lithium (inhibit hormone release)
- Amiodarone (destructive thyroiditis or iodine excess)
- Interferon-alfa (precipitate Hashimoto's thyroiditis)
- Iodine excess (iodinated contrast media, kelp, amiodarone)
- Propylthiouracil, methimazole
- Interference with thyroid hormone absorption in patients on replacement therapy (iron, calcium, chromium, phosphate binders, cholestyramine, colestipol)

Thyroiditis
- Subacute
- Silent (sporadic)
- Postpartum
- Amiodarone

Congenital defect in thyroid hormone synthesis

Central Hypothyroidism

Euthyroid sick syndrome

Pituitary disease
- Pituitary adenoma
- Hemorrhage
- Infiltrative (amyloid, sarcoid)

Hypothalamic disease

of the eyebrows may occur. The nails also become brittle and thin. The skin may take on a yellowish tinge from carotene, which accumulates because of impaired conversion to vitamin A. Carotenemia is distinguished from jaundice by the sparing of the conjunctiva. Vitiligo may occur in association with polyglandular syndrome, whereas hyperpigmentation may be seen if the patient has concomitant Addison's disease (Schmidt's syndrome).[62,68]

Generalized edema of the face and extremities may develop—nonpitting from accumulation of glycosaminoglycans and pitting from a capillary leak phenomenon seen in hypothyroidism. A localized pretibial myxedema and exophthalmos may still be seen in patients with Graves' disease rendered hypothyroid by surgery or radioactive iodine.[68]

The hypothyroid patient is usually normothermic, but complaints of cold intolerance and cool extremities are common. Blood pressure is usually normal, but 20 to 40% of patients have diastolic hypertension and narrowing of the pulse pressure. Bradycardia is common, but asymptomatic.[62,63] In contrast to hyperthyroidism, in which atrial arrhythmias are frequently seen, hypothyroidism may be associated with QT prolongation and ventricular irritability.[69,70] Patients with hypothyroidism often complain of dyspnea on exertion and decreased exercise capacity, and although decreased cardiac contractility and diastolic dysfunction is present in chronic hypothyroidism, signs of congestive heart failure are usually absent. Angina and coronary artery disease may be masked by slowed metabolism and decreased ischemic stress, but coronary disease is accelerated by elevations in cholesterol and blood pressure.[62,71]

Pericardial effusions may be seen in chronic hypothyroidism, but are usually small and asymptomatic. Larger effusions may result in diminished heart sounds and decreased apical impulse, but cardiac tamponade is rarely seen due to slow chronic build up.[72,73]

Complaints of fatigue, dyspnea, and decreased exercise capacity are most likely to be from a respiratory origin, rather than cardiac. Hypothyroidism is characterized by impaired ventilator responses to hypercapnea and hypoxia, as well as myopathy of respiratory musculature, with resultant slow, shallow respirations. Macroglossia may contribute to the respiratory distress and lead to obstructive sleep apnea. Mucopolysaccharide infiltration or edema of the vocal cords leads to a deep, husky voice in the hypothyroid patient. Primary pulmonary hypertension is reported with increased prevalence in hypothyroidism and may contribute to complaints of dyspnea or chest pain.[74,75]

A modest weight gain is characteristic of hypothyroidism, but massive obesity is unusual. Limiting the anticipated weight gain in this hypometabolic state is a concomitant decrease in appetite.[62]

Neurocognitive impairment may be a presenting feature of hypothyroidism, especially in elders. Slowness of comprehension, lethargy, decreased attention span, poor short-term memory, and impaired abstract thinking may all be present. The patient generally appears placid or depressed, moves slowly and deliberately, and speaks hesitantly.[76,77] Although unusual in hypothyroidism, extreme agitation, psychosis, and even seizures have been described—the last is referred to as myxedema madness or Hashimoto's encephalopathy.[42,78]

Paresthesias are common in hypothyroidism and although peripheral polyneuropathy may occur, mononeuropathies are much more prevalent. Edema of perineural and synovial tissue within the carpal tunnel leads to carpal tunnel syndrome, which is reported in about 25% of hypothyroid patients. Another common mononeuropathy in hypothyroidism involves the eighth cranial nerve, resulting in sensorineural hearing loss and tinnitus.[77]

Muscle-related symptoms are frequent in hypothyroid patients, often manifesting with proximal muscle weakness, myalgias, stiffness, and fatigue. Hypothyroid myopathy leads to slowing of the relaxation phase of deep tendon reflexes, referred to as hung-up or pseudomyotonic reflexes. This reflex phenomenon is best demonstrated with the Achilles tendon reflex performed while the patient is kneeling on a chair. Hung-up reflexes are not unique to hypothyroidism, as they can be seen with aging, diabetes, and pregnancy. Muscle palpation in most patients is normal, but some with hypothyroid myopathy develop firm, enlarged muscles referred to as pseudohypertrophy. Prolonged mounding of muscle mass may sometimes be evident when reflexes are elicited (myoedema). Ataxia and dysmetria reversible with thyroid replacement have been described, which may by myopathic or cerebellar in origin.[77,79]

Elevation of the serum creatine kinase (CK) concentration is seen in 70 to 90% of patients with hypothyroidism; however, the magnitude of the CK elevation does not correlate well with the severity of the patient's myopathy or hypothyroidism. Rare cases of acute rhabdomyolysis have been reported in severe

hypothyroidism, precipitated by exercise, statin therapy, or renal failure.[80]

One of the most common complaints of the hypothyroid patient is constipation, which results from decreased bowel motility. Rarely, ileus or megacolon may occur and be confused with intestinal obstruction.

Although oligo- or amenorrhea may suggest a pituitary/hypothalamic origin, primary hypothyroidism can result in menstrual abnormalities due to altered metabolism of estrogen. Menorrhagia is also described. Decreased fertility and early abortions are commonly associated complaints. Hypothyroid men often report decreased libido, erectile dysfunction, and delayed ejaculation.[62,63]

Initial symptoms of hypothyroidism may be rheumatic in character. Arthralgias and stiffness, sometimes associated with noninflammatory joint effusions, may be seen. Acute monoarthritis may be seen due to an increased prevalence of hyperuricemia and gout in hypothyroid patients, and perhaps as a result of a minor link with pseudogout and chondrocalcinosis as well[81,82] (Box 126-8).

Myxedema coma is a life-threatening decompensation of severe long-standing hypothyroidism, often precipitated by an acute illness or stress. The hallmarks of myxedema coma are altered mental status and hypothermia, but hypotension, bradycardia, and hypoventilation are often present as well. The typical patient is an elderly woman with chronic hypothyroidism that is untreated or unrecognized. Hashimoto's thyroiditis is the most common underlying thyroid pathology due to its insidious nature, but any cause of hypothyroidism is possible. The history is one of progressive weakness, lethargy, and immobility that may progress to shock and death.

Virtually any acute illness may precipitate myxedema coma, but the most common factors include infection, cold exposure, trauma, cerebrovascular accident, congestive heart failure, gastrointestinal bleeding, and drug effects. Sedatives and narcotics are commonly implicated drug classes, but general anesthesia, thyroid hormone noncompliance, amiodarone, lithium, iodides, phenytoin, and rifampin may be factors[33,63,75,83-85] (Box 126-9).

BOX 126-8 SYMPTOMS AND SIGNS OF HYPOTHYROIDISM

Vital Signs
Systolic BP—normal or low
Diastolic BP—normal or elevated
Slow pulse to sinus bradycardia
Respirations—normal or slow, shallow
Temperature—normal, but prone to hypothermia with stress

Hypometabolic Complaints
Cold intolerance
Fatigue
Weight gain, but decreased appetite

Cutaneous
Coarse, brittle hair
Alopecia
Dry skin, decreased perspiration
Pallor, cool hands and feet
Coarse, rough skin
Yellow tinge from carotenemia
Thin, brittle nails
Lateral thinning of the eyebrows

Neurologic
Slow mentation and speech
Impaired concentrating ability and attention span
Lethargy
Decreased short-term memory
Agitation, psychosis
Seizures
Ataxia, dysmetria
Mononeuropathy
  Carpal tunnel syndrome
  Sensorineural hearing loss
Peripheral neuropathy

Muscular
Proximal myopathy
Pseudohypertrophy
Delayed relaxation of reflexes (hung-up or pseudomyotonic)

Cardiac
Decreased exercise capacity
Dyspnea on exertion
Sinus bradycardia
Long QT with increased ventricular arrhythmia
Chest pain—accelerated coronary disease
Diastolic heart failure (delayed ventricular relaxation)
Pericardial effusion (asymptomatic)
Peripheral edema

Respiratory
Dyspnea on exertion
Obstructive sleep apnea
Primary pulmonary hypertension

Gastrointestinal
Constipation
Ileus
Gastric atrophy

Reproductive
Oligo- and amenorrhea
Menorrhagia
Decreased fertility
Early abortions
Decreased libido
Erectile dysfunction

Rheumatic
Polyarthralgias
Joint effusions
Acute gout or pseudogout

HEENT
Hoarseness
Deep, husky voice
Macroglossia
Hearing loss
Periorbital swelling
Broad nose
Swollen lips
Goiter

BP, blood pressure; HEENT, head, ear, eyes, nose, and throat.

BOX 126-9 MYXEDEMA COMA: AGGRAVATING OR PRECIPITATING FACTORS

Infection/sepsis (especially pneumonia)
Exposure to cold
Cerebrovascular accident
Drug effect
- *Altered sensorium:* Sedative-hypnotics, narcotics, anesthesia, neuroleptics
- Decrease T_4 and T_3 release: amiodarone, lithium, iodides
- Enhance elimination of T_4 and T_3: phenytion, rifampin
- *Inadequate thyroid hormone replacement:* Noncompliance; interference with absorption (iron, calcium, cholestyramine)

Myocardial infarction
Gastrointestinal bleeding
Trauma/burns
Congestive heart failure
Hypoxia
Hypercapnia
Hyponatremia
Hypoglycemia
Hypercalcemia
Diabetic ketoacidosis

T_3, triiodothyronine; T_4, thyroxine.

BOX 126-10 RECOGNITION OF MYXEDEMA COMA

Patient profile: Elderly female in the winter
Known hypothyroidism; thyroidectomy scar
Hypothermia: Usually below 95.9° F; below 90° F is bad prognostic sign; as low as 75° F reported. Near normal in presence of infection
Altered mental status: Lethargy and confusion to stupor and coma, agitation, psychosis and seizures (myxedema madness)
Hypotension: Refractory to volume resuscitation and pressors unless thyroid hormone administered
Slow, shallow respirations with hypercapnea and hypoxia; high risk of respiratory failure
Bradycardia (sinus)/long QT and ventricular arrhythmias
Myxedema facies: Puffy eyelids and lips, large tongue, broad nose
Evidence of severe chronic hypothyroidism: Skin, hair, reflexes, bradykinesis, voice
Acute precipitating illness (e.g., pneumonia)
Drug toxicity (e.g., sedative, narcotic, neuroleptic)
Hyponatremia

It is important to appreciate that although infection is the most common precipitant of myxedema coma, the patient does not usually mount a febrile response due to the profound hypometabolic state. Peripheral vasoconstriction helps maintain core temperature in severe hypothyroidism, but this compensation may be tenuous. Hypothermia is characteristic of myxedema coma and it is usually marked, with body temperatures as low as 24° C (75° F) described. Temperatures below 90° F are common and carry a grave prognosis. In contrast to environmental hypothermia, shivering is often absent.[63,75,85]

Whereas diastolic hypertension is common in hypothyroidism, the blood pressure in myxedema coma is usually low and may be refractory to fluid resuscitation and pressors unless thyroid hormone is administered.[75] Sinus bradycardia is routinely seen and may be unresponsive to atropine, but heart block is unusual. Prolongation of the QT interval with cases of torsades de pointes is described.[70] Despite cardiac enlargement and decreased myocardial contractility seen in most patients, evidence of congestive heart failure is not common.[62]

Signs of severe hypothyroidism are usually evident in the myxedema coma patient. Dry, coarse skin; sparse, brittle hair; cool extremities; puffy eyelids and face; large tongue; hoarse voice; and slow, delayed speech and movement are typical. Pitting and nonpitting edema are prominent in the extremities.[68] Pleural and pericaridial effusions are common, and ascites may be present.[86]

Despite the name myxedema coma, most patients present with confusion, lethargy, or stupor and are not comatose, but progression to coma is inexorable if therapy is not instituted. The cause of altered mental status is multifactorial, including thyroid hormone deficiency, hypothermia, hypercapnea, hyponatremia, hypotension, and hypoglycemia.[75,83] Paradoxically, a more agitated, psychotic state may sometimes occur, referred to as myxedema madness.[77] Focal or generalized seizures may occur in up to 25% of patients, and status epilepticus has been reported.[78]

Respiratory depression with carbon dioxide retention is common in myxedema coma, contributing further to the altered mental status. An enlarged tongue, supraglottic edema, and obesity further aggravate hypercapnea and hypoxia. Pneumonia, a common precipitant of myxedema coma, accelerates the downward spiral toward respiratory failure. Mechanically assisted ventilation is required in most patients, often leading to extended hospitalization[74,85] (Box 126-10).

Diagnostic Strategies

The diagnosis of primary hypothyroidism requires the measurement of an elevated serum TSH and a depressed free T_4 level. If the index of suspicion is low, the serum TSH alone can be used as a screening test, and the free T_4 test only performed if the TSH is abnormal. The total T_4 level is not recommended in evaluating thyroid disease because of numerous confounding factors on protein binding that alter its measurement, thus the free T_4 is preferred. The serum T_3, whether total or free, should not be relied on in the diagnosis hypothyroidism due to its great variability. Almost any acute or chronic illness or physiologic stress can lead to depression of T_4 5′-deiodinase activity, thereby leading to decreased peripheral conversion of T_4 to T_3 and an increase in reverse T_3 levels.[7]

The elevation of TSH accompanied by a normal free T_4 is referred to as subclinical hypothyroidism (SCH). The prevalence of SCH is 4 to 9% in large general population screening surveys and in 7 to 26% in geriatric series.[1,2,62,87] Although by definition SCH is asymptomatic, this laboratory abnormality is associated with the development of depression, cognitive impairment, subtle systolic and diastolic dysfunction, and hyperlipidemia.[88]

The distinction of myxedema coma from moderate to severe hypothyroidism cannot be made by thyroid functions tests alone. Elevation of the serum TSH may be blunted by any concomitant systemic illness (hypothyroid sick syndrome), resulting in a misleadingly minor elevation in TSH in a severely hypothyroid patient. Central hypothyroidism is characterized by a low serum TSH together with a low free T_4 level. The euthyroid sick syndrome can have very similar results but the TSH is only mildly suppressed and the free T_4 is normal or slightly low. Because central hypothyroidism is usually not a chronic condition, many of the clinical findings of hypothyroidism are absent.[67,75,88]

Hyponatremia is a common electrolyte abnormality in severe hypothyroidism and myxedema coma, but it is not seen in milder forms of the disease. Hyponatremia results from decreased free water clearance due to diminished renal blood flow from volume depletion and depressed cardiac output as well as excess excretion of anti-diuretic hormone. A reversible elevation in serum creatinine is also seen in this setting.[62,75,84]

Hypoglycemia may also occur in severe hypothyroidism and myxedema coma. Decreased gluconeogenesis and reduced insulin clearance are the likely mechanisms, but it is important to recognize that a low blood sugar may be a clue of concomitant adrenal insufficiency, which is present in up to 10% of myxedema coma patients.

CK from a muscular origin is often elevated in severe hypothyroidism, but acute rhabdomyolysis is uncommon.[80] Serum transaminases and lactate dehydrogenase are frequently elevated as well.

Lipid clearance is decreased in hypothyroidism, resulting in elevations of total cholesterol, low density lipoprotein, and triglyceride. In the Colorado Thyroid Disease Prevalence Study of 25,862 patients, euthyroid patients averaged a total cholesterol of 214 mg/dL, whereas subclinical and overt hypothyroid subjects averaged 224 and 251 mg/dL, respectively.[1-3]

Severe hypothyroidism may be associated with a normocytic, normochromic anemia from decreased red cell production and a depressed white blood count that does not rise appropriately in response to infection.[75] Increased bleeding times may result from an acquired von Willebrand's syndrome.

A chest radiograph may reveal an enlarged cardiac silhouette, but evidence of heart failure is unusual. Although myocardial hypertrophy may be present in hypothyroidism, cardiomegaly usually represents the presence of pericardial effusion, seen in 30 to 78% of severe, chronic disease, but less than 5% of mild hypothyroidism. Pleural effusions may be seen as well.[62,72,73,75]

Electrocardiographic findings include sinus bradycardia, nonspecific ST and T wave abnormalities, and decreased voltage or electrical alternans if a pericardial effusion is present. Prolongation of the QT interval and ventricular arrhythmias may be seen as well.[69,70,75]

If a lumbar puncture is performed to evaluate altered mental status, findings of increased opening pressure and an elevated cerebrospinal fluid protein level may be seen in myxedema coma.

Differential Considerations

The overtly hypothyroid patient is often thought to be severely depressed, and the diagnosis of hypothyroidism may be overlooked. In fact, about 10 to 15% of patients hospitalized for depression are found to be hypothyroid. Roughly 25% of bipolar patients with a rapid cycling pattern are found to be hypothyroid. Even subclinical hypothyroid patients have more than twice the incidence of depression than euthyroid patients.[76] The profound fatigue and weakness that may occur in hypothyroidism may be diagnosed as depression, chronic fatigue syndrome, Addison's disease, or anemia.

Respiratory failure in patients with substrates of obstructive sleep apnea such as obesity, hypoventilation, and macroglossia, should be evaluated for hypothyroidism. In addition, any patient with decreasing exercise capacity and dyspnea without any clear cardiopulmonary cause should be evaluated for hypothyroidism.

The hypothermia of myxedema coma may be attributed to environmental stress, sepsis, or hypoglycemia. The altered mental status, as well, may be attributed to concomitant conditions in myxedema coma, such as drug toxicity, hypothermia, hypercapnea, hypoxia, hypoglycemia, or hyponatremia, and the hypothyroidism overlooked.

Management

The patient with a new diagnosis of overt or subclinical hypothyroidism generally does not require the initiation of treatment from the emergency department, yet it is important to be familiar with the principles of diagnosis and treatment. Before commitment to lifelong therapy, the serum TSH and free T_4 should be repeated for confirmation. About 5% of patients with subclinical hypothyroidism normalize within 1 year and, of the remainder, approximately 5% per year develop overt hypothyroidism. Treatment with thyroid hormone replacement may be considered in SCH if symptomatic or the TSH is greater than 10.[62,64,88]

Levothyroxine (T_4) is the mainstay of treatment of hypothyroidism. Treatment is generally started at a dose of 1.6 μg/kg/day in younger patients, whereas elders and patients with underlying coronary artery disease are often started at less than half that dosage due to their susceptibility to angina and arrhythmias. The long half-life of T_4 (7 days) and its gradual conversion to T_3, leads to dosage adjustments of 12.5- to 25-μg increments at no less than 6-week intervals.[62,63]

The management of myxedema coma requires immediate attention to airway management, fluid resuscitation, thyroid hormone replacement, general supportive measures, and treatment of the precipitating illness (Box 126-11).

BOX 126-11 TREATMENT OF MYXEDEMA COMA

- Protect the airway/ventilatory support; monitor for alkalosis
- Fluid resuscitation:
  - 0.9NS or D_5/0.9NS if hypoglycemia
  - Watch for unmasking of CHF
- Thyroid hormone replacement:
  - T_4 alone (elderly and patients with cardiac comorbidity):
    - T_4 300–500 μg IV as initial bolus
    - Or split bolus 200–300 μg IV day 1 and 2
    - Then 50–100 μg IV daily until able to take PO
  - T_3 alone (younger patient, no cardiac risks; rapid correction desired):
    - T_3 10–20 μg IV initially, then 10 μg IV every 4 hr for 1 day, then 10 μg IV every 6 hr for 1–2 days
  - Combination T_4 and T_3 therapy (intermediate approach):
    - T_4 200–250 μg IV as initial bolus
    - T_3 10 μg IV initial dose, then 10 μg IV every 8–12 hr
    - T_4 100 μg IV in 24 hr, followed by 50 μg/day
- Hydrocortisone
  - 50–100 mg IV every 6–8 hr
- Hyponatremia
  - Avoid hypotonic fluids, use only 0.9NS or D_5/0.9NS
  - If less than 120 mEq/L, consider 3% saline, 50–100 mL boluses
- Passive rewarming
  - Regular blankets, prevent heat loss
  - If heating blankets considered, pretreat with IV fluids and monitor BP closely
  - Avoid mechanical stimulation
- Treatment of any precipitating illness, with special attention to infectious causes

BP, blood pressure; CHF, congestive heart failure; D_5/0.9NS, 5% dextrose in 0.9% normal saline; IV, intravenous; T_3, triiodothyronine; T_4, thyroxine.

Airway Management

Prompt attention to the airway is critical, as there may be partial obstruction from macroglossia and supraglottic edema, myopathy of respiratory muscles, and central hypoventilation. Most myxedema coma patients require endotracheal intubation and prolonged ventilatory support. Blood gases should be monitored closely as life-threatening alkalosis can occur during the initial phase of full ventilator support.[74]

Fluid Resuscitation

Intravascular volume depletion is prominent in myxedema coma, even in the presence of normal vital signs. Fluid resuscitation should be started immediately, but the aggressiveness of administration should be tempered by the risk of unmasking congestive heart failure. The initial fluid of choice is D_5/0.9NS because the myxedema coma patient is at high risk for both hyponatremia and hypoglycemia.[75,83-85]

Thyroid Hormone Replacement

Prompt thyroid hormone replacement is critical for patient survival from myxedema coma, although the most effective regimen is unclear. Determination of the form of thyroid hormone (T_4 or T_3 or both) and the dosage must balance the high mortality of untreated myxedema coma against the risk of myocardial infarction or cardiac arrhythmias induced by therapy. T_4 has lower risk of toxicity as its action depends on peripheral conversion to T_3, which is a slow, delayed process. Proponents of T_3 administration suggest that the quicker onset of action and the increased biologic activity of T_3, as well as the impaired conversion of T_4 to T_3 in the critically ill, make T_3 the logical choice. High doses of T_4 or T_3 appear to increase mortality, hence there is a limit on how fast hormone replacement can be given.[33,63,75,83-85]

The most widely published approach to myxedema coma involves the IV administration of T_4 in a dose of 300 to 500 µg that depends on patient weight and cardiac risks. It is suggested that this dose replaces total body stores of T_4, and the pool can be maintained by 50 to 100 µg/day. Some authors suggest splitting the loading dose over 2 days.[75,83,84]

For critically ill younger patients without cardiac disease, where a more rapid correction of hormone levels is desired, the use of T_3 alone should be considered. An IV loading dose of 10 to 20 µg, followed by 10 µg IV every 4 hours for 24 hours, followed by 10 µg every 6 hours for 1 to 2 days is suggested.[75]

An intermediate approach using both T_4 and T_3 is suggested by some authors to speed clinical response while minimizing cardiac toxicity. T_4 is administered IV in half the loading dose (200–250 µg) with 10 µg of T_3, followed by T_3, 10 µg every 8 to 12 hours, and maintenance T_4, 50 µg every 24 hours. Due to impaired oral absorption and transit of medications in myxedema coma, the IV route is recommended until the patient is alert and able to tolerate oral intake, and then maintenance T_4 alone is continued.[75,83]

General Supportive Measures

The management of hyponatremia in myxedema coma requires water restriction, but in the face of the volume depletion and hypotension seen in myxedema coma, normal saline solutions should be used. If hyponatremia is severe (<120 mEq/L), hypertonic saline in 50- to 100-mL boluses should be considered.[75,83,84]

Hydrocortisone should be administered to all patients in myxedema coma. A small proportion of these patients may have central hypothyroidism where concomitant adrenocorticotropic hormone (ACTH) deficiency may be present. Another subset may have autoimmune destruction of both the thyroid and adrenal glands (Schmidt syndrome). Most patients are presumed to suffer from relative adrenal insufficiency unmasked by stress and the enhanced clearance of cortisol. Hydrocortisone is given IV, 50 to 100 mg, every 6 to 8 hours for several days.[75]

Hypothermia is treated with passive rewarming, using regular blankets and prevention of further heat loss. Heating blankets could be employed, but there is risk that the resulting vasodilation will lead to a fall in peripheral vascular resistance and hypotension. As in accidental hypothermia, excessive mechanical stimulation should be avoided due to risk of precipitating arrhythmias.

Identification and Treatment of Precipitating Illness

Concomitant with the previous treatment measures, a precipitating illness for myxedema coma should be sought and treated aggressively with special attention paid to a potential infectious cause, which accounts for about one third of cases.[89,90]

Without thyroid hormone replacement and a vigorous approach, the mortality rate from myxedema coma exceeds 80%; but with the comprehensive approach described and monitoring in the intensive care unit, the mortality rate falls to 20% or less. Factors that predict a poor outcome in myxedema coma include advanced age, a body temperature of less than 90° F or hypothermia refractory to treatment, hypotension, pulse less than 44 beats per minute, and sepsis.[91-93]

ADRENAL INSUFFICIENCY

Perspective

Adrenal insufficiency in its chronic form is an uncommon disease with nonspecific symptoms that include fatigue, weakness, weight loss, depression, and nonspecific gastrointestinal symptoms. This presentation is difficult to diagnose on a single encounter, yet recognition is critical as an acute superimposed stress can lead to vascular collapse and death. The acute development of severe adrenal insufficiency de novo can also occur and be life-threatening. Both the acute and chronic forms of adrenal insufficiency can be primary, due to adrenal gland destruction, or secondary, caused by pituitary gland failure to produce ACTH. Recognition of acute adrenal insufficiency and prompt administration of hydrocortisone is critical to patient survival.[94-97]

Principles of Disease

The adrenal cortex produces cortisol, aldosterone, and androgens, and the adrenal medulla produces catecholamines. Primary adrenal failure leads to a deficit of cortisol and aldosterone only, but catecholamine and androgen production continues from other sites. Secondary adrenal failure is related to decreased production of ACTH from the pituitary gland and as a result, only cortisol deficiency develops, as aldosterone is regulated by the rennin-angiotensin system. Cortisol has numerous actions that include facilitating gluconeogenesis and lipolysis, inhibiting insulin secretion, anti-inflammatory actions, immune-modulating effects, augmenting vascular reactivity to vasoconstrictors, promoting catecholamine synthesis, and retarding bone growth.[94,96,97] Aldosterone acts primarily at the distal nephron where it promotes the reabsorption of sodium and the excretion of potassium and hydrogen. A deficiency of cortisol alone may lead to blood pressure lower-

ing, but the loss of both cortisol and aldosterone causes a greater hypotensive effect.[96]

Etiology

Primary failure of the adrenal gland is referred to as Addison's disease, and the majority of such cases in the Western world are due to autoimmune adrenalitis, with about half of these being isolated deficiencies and the other half associated with a polyglandular autoimmune syndrome (PGA). There are two variants of the PGA: PGA type I is a rare autosomal recessive condition consisting of Addison's disease, hypoparathyroidism, chronic mucocutaneous candidiasis, and vitiligo. PGA type II (Schmidt's syndrome), the predominant form, includes primarily Addison's disease and hypothyroidism, as well as diabetes and hypogonadism[94-97] (Box 126-12).

Destruction of the adrenal glands by tuberculosis is the most common cause of Addison's disease worldwide, but is rare now in the United States except when associated with AIDS. Other disseminated infections such as cryptococcosis, histoplasmosis, blastomycosis, CMV, toxoplasmosis, and lung disease from *Mycobacterium avium-intercellulare*, and *Pneumocystis* may result in adrenalitis and Addison's disease, but these too are seen almost exclusively in the setting of HIV infection. Infiltration with Kaposi's sarcoma and direct involvement by HIV alone may lead to adrenal insufficiency, and overall, about 20% of HIV patients who are critically ill have laboratory evidence of cortisol deficiency.[98]

Adrenal metastases, most commonly from lung and breast cancer, are often found at autopsy, but symptomatic adrenal insufficiency is seen in only about 4% of these patients, probably because over 90% of both adrenals must be destroyed before function is affected. Infiltration of the adrenals by nonmalignant processes, such as sarcoid, amyloid, and hemochromatosis may also lead to Addison's disease.[96,97]

Drug therapy may precipitate or unmask adrenal insufficiency. The most noteworthy cause is etomidate, an imidazole agent used in the induction and maintenance of anesthesia. Etomidate blocks cortisol synthesis by inhibiting the 11β-hydroxylase enzyme. Etomidate infusions in an intensive care setting have been associated with acute adrenal insufficiency and are not recommended, but bolus administration for rapid sequence intubation appears safe, yet rare cases of crisis have been described.[99,100] Adrenal inhibition subsequent to a single etomidate bolus can be demonstrated in 80% of patients in the first 12 hours, and about one half at the 24-hour mark, followed by rapid resolution by 48 hours.[101] Trends toward hypotension and pressor use have been demonstrated in trauma patients admitted to an intensive care unit who have received rapid sequence intubation with etomidate, but a cause-and-effect relationship is difficult to assess. Other drugs that may aggravate adrenal insufficiency include ketoconazole (inhibits cortisol synthesis), rifampicin (increases cortisol catabolism), and megastrol acetate (stimulates the glucocorticoid receptor and suppresses ACTH).[102]

The presentation of hypoadrenalism in childhood often suggests an inherited disorder such as PGA syndromes, adrenoleukodystrophy, adrenal hypoplasia, or ACTH unresponsiveness.[96,97]

The development of bilateral hemorrhagic infarction of previously normal adrenal glands can result in acute adrenal insufficiency, carrying a very high mortality rate. Meningococcal sepsis (Waterhouse-Friderichsen syndrome) is classically described, but infections with *Pseudomonas*, *Escherichia coli*, group A *Streptococcus*, *Pneumococcus*, and *Staphylococcus* can result in a similar syndrome.[103]

Adrenal hemorrhage or infarction from coagulopathies can also result in acute adrenal insufficiency if 90% of both glands are involved. Warfarin or heparin anticoagulation in excess or during severe stress can result in hemorrhage that leads to acute crisis.[104] Venous infarction of the adrenals resulting in addisonian crisis has been described in the antiphospholipid antibody syndrome, and in one series it was the presenting manifestation of the disease in 36% of patients.[105] Adrenal hemorrhage has also been described in blunt thoracoabdominal trauma, but although associated liver, spleen, and kidney injuries are common, adrenal insufficiency is rare.[106]

Acute and chronic hypoadrenalism may also result from ACTH deficiency, in which exogenous glucocorticoid therapy is the most common cause. Reduced responsiveness and possible atrophy of the adrenal gland can be anticipated whenever supraphysiologic doses of a glucocorticoid (hydrocortisone 30 mg, prednisone 7.5 mg, or dexamethasone 0.75 mg daily) are taken for more than 3 weeks, but as little as 5 days is required if the daily dose exceeds the equivalent of 20 mg of prednisone.[94,96,97] Inhibition of ACTH secretion depends not only on the dose and duration of therapy but also on the frequency and timing of the dose, such that more than once per day and any evening dose have a much greater suppressive

BOX 126-12 CAUSES OF ADRENAL INSUFFICIENCY

Primary Adrenal Insufficiency

Chronic

Autoimmune adrenalitis (Addison's disease)—isolated or polyglandular deficiency, HIV infection (direct involvement or disseminated CMV, MAI, TB, cryptococcosis, histoplasmosis, blastomycosis, toxoplasmosis, *Pneumocystis* pneumonia)
TB and disseminated infections as seen with HIV
Metastatic cancer (breast, lung)
Infiltrative (sarcoid, hemochromatosis, amyloid)
Congenital (adrenal hypoplasia, adrenoleukodystrophy, ACTH resistance)
Bilateral adrenalectomy
Drug toxicity (etomidate, ketoconazole, rifampicin)

Acute

Adrenal hemorrhage
  Meningicoccemia and other sepsis
  Anticoagulation (heparins and warfarin)
  Anticardiolipin antibody syndrome
  Trauma

Secondary Adrenal Failure

Chronic

Pituitary tumor (primary or metastatic)
Pituitary surgery or irradiation
Chronic steroid use with functional deficiency
Infiltrative (sarcoid, eosinophilic granuloma, TB)
Traumatic brain injury
Postpartum pituitary necrosis (Sheehan's syndrome)
Empty sella syndrome

Acute

Pituitary apoplexy (hemorrhage into a pituitary tumor)
Postpartum pituitary necrosis (Sheehan's syndrome)
Traumatic brain injury
Relative adrenal insufficiency (sepsis, hepatic failure, severe acute pancreatitis, trauma)

ACTH, adrenocorticotropic hormone; CMV, cytomegalovirus; HIV, human immunodeficiency virus; MAI, *Mycobacterium avium-intracellulare*; TB, tuberculosis.

effect on pituitary ACTH, even if by the inhalational route.[107]

Other causes of secondary adrenal insufficiency result from direct destruction of the pituitary gland. Chronic hypopituitarism can result from pituitary adenomas or metastatic involvement, surgical hypophysectomy or pituitary irradiation, and granulomatous disease of the pituitary (sarcoid, tuberculosis, eosinophilic granuloma).[66]

Acute onset of secondary adrenal insufficiency can result from hemorrhage into a pituitary adenoma, referred to as pituitary apoplexy. Ischemic necrosis of the pituitary associated with hypotension, most commonly in the postpartum period (Sheehan's syndrome), can result in either acute or chronic hypoadrenalism and hypopituitarism.[108]

Traumatic brain injury is an increasingly recognized cause of central hypoadrenalism. In a compilation of 710 patients, the majority of whom presented with a Glasgow Coma Score of 3 to 13, 13% developed ACTH deficiency, many were evident in the initial hospitalization, but some presented up to 6 months after injury. Similar percentages were seen for growth hormone and gonadotropin deficiencies.[109,110]

Functional adrenal insufficiency, another central cause of hypoadrenalism, occurs in critically ill patients who have an inability to mount an adequate ACTH and cortisol response to sepsis or overwhelming stress, leading to increased mortality during the acute illness. Looking specifically at septic shock, more than 50% of patients have evidence of this relative adrenal insufficiency.[111-114]

Symptoms and Signs

The presentation of Addison's disease and other causes of chronic primary adrenal gland failure is often vague and nonspecific, with the insidious onset of fatigue, generalized weakness, and weight loss. Gastrointestinal symptoms are common with nausea, intermittent vomiting, abdominal pain, and diarrhea or constipation.[115] Low-grade fever, arthralgias, and muscle cramps suggest a persistent flulike syndrome. Salt craving, sometimes with massive salt ingestion, and postural dizziness or syncope result from concomitant mineralocorticoid deficiency. Psychiatric symptoms occur early in the disease and may predate other symptoms. The most common presentations include depression, manifested by apathy and lack of initiative, memory impairment that can progress to confusion and delirium, a dementia-like picture, and psychosis[94-97] (Box 126-13).

Adrenal insufficiency due to ACTH deficiency may present with similar symptoms, but salt craving and postural hypotension are absent because the renin-aldosterone axis remains intact. Symptoms often relate more to deficiency of pituitary hormones other than ACTH, specifically follicle-stimulating hormone/luteinizing hormone, resulting in loss of libido, infertility, amenorrhea, and TSH with cold intolerance and weight gain.[66,94,96]

In most cases Addison's disease is not recognized until an acute intercurrent illness precipitates a crisis, but some clinical clues may alert the clinician to the diagnosis. The systolic blood pressure is usually below 110 mm Hg, and postural changes may be found. Hyperpigmentation of sun-exposed areas, palmar creases, nipples, axillae, recent scars, and all mucous membranes is typically seen in Addison's disease, due to compensatory elevation of ACTH, which in turn stimulates melanocyte receptors to produce melanin. In women, loss of adrenal androgen can lead to thinning of pubic and axillary hair. Patients with secondary adrenal insufficiency lack hyperpigmentation and hypotension, and thus the condition is more difficult to identify. Vitiligo may be seen in 10 to 20% of patients with Addison's disease associated with polyglandular autoimmune syndrome I. Auricular cartilage calcification is an unexplained phenomenon seen in men with either chronic primary or secondary adrenal insufficiency.[116,117]

BOX 126-13 Clinical Features of Adrenal Insufficiency

General	
Weakness, fatigue	100%
Anorexia	100%
Gastrointestinal symptoms	92%
Weight loss	100%
Hyponatremia	90%
Blood pressure ≤110/70 mm Hg	88–94%
Fevers (mild)	Common
Depression, apathy	20–40%
Myalgia, arthralgias	6–13%
Auricular calcifications	5%
Primary	
Hyperpigmentation	94–97%
Salt craving	16–22%
Orthostasis, syncope	12–16%
Vitiligo	10%
Hyperkalemia	65%
Hyperchloremia and acidosis	65%
Hypoglycemia	Mild, occasional
Secondary	
Hyperkalemia	Not present
Hyperpigmentation	Not present
Hypoglycemia	More severe, common
Orthostasis, hypotension	Uncommon
Amenorrhea	Common
Axillary and pubic hair loss	Occasional
Decreased libido	Occasional
Crisis	
Refractory hypotension	100%

Most adrenal crises occur in the setting of chronic adrenal insufficiency in which almost any acute intercurrrent illness or stress overwhelms the patients limited cortisol reserve. Less common, but a more fulminant presentation, is acute adrenal or pituitary hemorrhage or infarction.[104,105,108]

The presentation of acute adrenal insufficiency can vary from a picture suggesting acute gastroenteritis with nausea, vomiting, fever, and dehydration to sudden vascular collapse and death. The cardinal feature of adrenal crisis is hypotension or shock out of proportion to the severity of the current illness. Despite aggressive fluid resuscitation, the blood pressure typically shows little response and is often refractory to pressors.[94-96]

Abdominal pain may be a presenting symptom, mimicking an acute abdomen, this picture being particularly dramatic with acute adrenal hemorrhage or infarction. Hypotension accompanying sudden severe headache and visual field cuts suggests acute pituitary apoplexy.

Diagnostic Strategies

The diagnostic approach to adrenal insufficiency depends on whether you are screening for a chronic condition or evaluating an acutely ill or critical patient, but in all circumstances the serum cortisol measurement is the mainstay. Serum cortisol has a diurnal variation, peaking between 6 and 8 AM, and reaching a nadir in the late evening and during early sleep. Screening the patient who is not acutely ill starts with an AM cortisol

measurement, which is normally between 10 and 20 µg/dL. An AM cortisol level above 20 µg/dL excludes hypoadrenalism, while a level below 3 µg/dL is diagnostic. Measurements between 3 and 10 µg/dL are strongly suggestive, but require confirmation with an ACTH (cosyntropin) stimulation test, and if the clinical suspicion is high, any patient with a level less than 20 µg/dL should have a stimulation test. This test can be performed any time of the day and involves obtaining a baseline cortisol, then administering 250 µg of ACTH as an IV bolus, followed by repeat serum cortisol levels at 30 or 60 minutes. The post-ACTH cortisol should exceed 20 µg/dL to exclude the diagnosis. If hypoadrenalism is confirmed, an AM ACTH level can be used to distinguish primary from central, a high ACTH being consistent with primary causes and a low or normal ACTH seen in secondary ones.[95,96] An ACTH stimulation test is the gold standard for diagnosing adrenal insufficiency, but it may be normal in the unusual circumstance of partial pituitary insufficiency. If such a possibility exists, measurement of ACTH in response to metapyrone or hypoglycemia could be performed by the endocrinologist. Another option is the measurement of plasma renin and aldosterone. Their values should be normal in secondary hypoadrenalism, whereas primary adrenal failure results in a decreased plasma aldosterone and an elevated plasma renin (Table 126-3).

If the patient is acutely ill, the physiologic stress should result in an elevation of serum cortisol regardless of the time of the day, such that a random level is adequate. If a patient is acutely ill, a cortisol level below 15 µg/dL is presumptive evidence of hypoadrenalism. Consensus opinion suggests that a random level greater than 33 µg/dL excludes the diagnosis in the acutely stressed patient. For serum cortisol measurements between 15 and 33 µg/dL, the patient should be treated presumptively with IV hydrocortisone. If an ACTH stimulation test can be performed, a rise in serum cortisol less than 9 µg/dL from the prestimulation level is diagnostic of adrenal insufficiency. The relative adrenal insufficiency of sepsis and other critical illness should be suggested if a random cortisol level is less than 25 µg/dL, and treatment should not be delayed awaiting confirmation by a stimulation test.[111-114]

Hyponatremia is seen in about 90% of patients with chronic primary adrenal insufficiency.[116,117] It is usually of mild to moderate severity, seldom below 120 mEq/L. Adrenal gland failure leads to aldosterone deficiency, which results in sodium loss. In addition, cortisol deficiency leads to increased antidiuretic hormone secretion and excess water reabsorption. Although aldosterone is not deficient in secondary adrenal insufficiency, increased antidiuretic hormone secretion alone results in hyponatremia in about 50% of patients and it may be severe. In hypoadrenalism of either cause, the administration of hydrocortisone suppresses antidiuretic hormone production and can correct hyponatremia.[96,97]

Due to aldosterone deficiency, hyperkalemia is seen in about two thirds of patients with primary adrenal insufficiency, but it is absent in secondary causes where aldosterone production is not affected. Serum potassium elevation is usually mild in Addison's disease and rarely exceeds 7 mEq/L. A mild hyperchloremic metabolic acidosis usually accompanies the elevated potassium due to impaired exchange of sodium with hydrogen and potassium when aldosterone is deficient.[96,97,116,117]

Older reviews describe fasting hypoglycemia in more than two thirds of patients with Addison's disease, whereas more recent literature suggests that hypoglycemia is more pronounced in secondary adrenal insufficiency and is often the presenting manifestation. Inhibition of gluconeogenesis resulting from cortisol deficiency, as well as reduced calorie intake and depletion of glycogen stores, makes adrenal insufficiency a set-up for hypoglycemia.[96,116] Deficiency of growth hormone and ACTH in hypopituitarism further increases the propensity to and severity of hypoglycemia.[66] Patients with type I diabetes and adrenal insufficiency often present with unexplained recurrent hypoglycemic reactions.[118]

Other laboratory abnormalities seen in adrenal insufficiency include hypercalcemia in about 6%, elevated BUN and creatinine in 55%, anemia in 40%, and eosinophilia in 17%.[96,97,116,117] Evaluation of the etiology of hypoadrenalism is usually beyond the scope of the emergency physician, but abdominal computed tomography may reveal adrenal hemorrhage, infarction, or metastatic disease, while computed tomography of the brain may demonstrate pituitary hemorrhage, tumor, or empty sella.[119]

Table 126-3 Diagnosis of Hypoadrenal States

	LEVEL (µg/dL)	DIAGNOSTIC CONCLUSION
Chronic, Nonstressed		
Serum cortisol (6–8 AM)	<3	Diagnostic
	<10	Suggestive
	10–20	Normal
	>20	Excludes
ACTH stimulation test (peak)	<20	Diagnostic
	>20	Excludes
Acute Crisis		
Serum cortisol (random)	<15	Diagnostic
	15–33	Indeterminant
	>33	Excludes
ACTH stimulation test (delta)	<9	Diagnostic
Relative Hypoadrenalism of Sepsis and Critical Illness		
Serum cortisol (random)	<25	Likely
ACTH stimulation test (delta)	<9	Diagnostic

Differential Diagnosis

Chronic adrenal insufficiency may be marked by wasting suggestive of anorexia nervosa or occult carcinoma. Generalized weakness, fatigue, and myalgias resemble chronic fatigue syndrome, polymyalgia rheumatic, myopathy, hypothyroidism, or flu syndromes.

Acute adrenal crisis with refractory hypotension often leads to a search for sepsis, gastrointestinal bleeding, myocardial ischemia, or anaphylaxis. Abdominal pain in crisis may mimic an acute abdomen especially if precipitated by adrenal hemorrhage. The headache and visual field cuts in pituitary apoplexy may resemble a hemorrhagic stroke.

Steroid withdrawal syndrome should be distinguished from adrenal insufficiency as both can occur with the cessation of chronic glucocorticoid therapy. Steroid withdrawal syndrome is characterized by symptoms that resemble chronic adrenal insufficiency, including weakness, malaise, fatigue, nausea, dizziness, and arthralgias. Patients with steroid withdrawal syndrome, however, are not predisposed to adrenal crisis as their hypothalamic-pituitary-adrenal axis is intact by ACTH stimulation testing.[96]

Management

Acute adrenal insufficiency and relative adrenal insufficiency of sepsis and critical illness are life-threatening conditions in which aggressive fluid resuscitation, hydrocortisone replacement, and treatment of any precipitating illness are the main-

BOX 126-14 TREATMENT OF HYPOADRENALISM

Maintenance
Hydrocortisone 20 mg AM, 10 mg PM
Fludrocortisone 100 µg/day

Maintenance during Minor Illness
Hydrocortisone 40 mg AM, 20 mg PM
Fludrocortisone 100 µg daily

Coverage during Procedural Stress
Hydrocortisone 100 mg IV (one time only)

Adrenal Crisis or Relative Adrenal Insufficiency of Critical Illness
Hydrocortisone 50–100 mg IV every 6 hr
OR
Hydrocortisone 50–100 mg IV followed by an infusion,
20 mg/hr
0.9 NS 2–3 L over the first few hours
Switch to D_5 NS if hypoglycemia
Treat precipitating illness

D_5 NS, 5% dextrose in normal saline.

stays of treatment. IV access should be established with two large-bore IVs and 2 to 3 L of 0.9% saline should be infused over the first few hours, monitoring for signs of fluid overload and blood pressure response. A bedside glucose should be determined due to the frequent incidence of hypoglycemia and 5% dextrose in normal saline substituted if indicated. Hypotonic fluids should be avoided as the frequency of hyponatremia is high. Bicarbonate is not required for the correction of acidosis and hyperkalemia, as rapid correction is generally seen with saline and hydrocortisone administration[95,96,120-122] (Box 126-14).

Blood should be drawn for random serum cortisol and ACTH, as well as electrolytes, but hydrocortisone treatment should not be withheld awaiting laboratory confirmation. Hydrocortisone is the glucocorticoid of choice as it has intrinsic mineralocorticoid properties, which obviates the need to administer a mineralocorticoid separately. Dexamethasone should not be used in this acute setting, as it has no mineralocorticoid effects. In a nonacute setting, dexamethasone is often suggested for glucocorticoid replacement while an ACTH stimulation test is being performed since it does not interfere with cortisol measurements. In a critical patient with possible adrenal insufficiency, an ACTH stimulation test is not recommended due to inherent delays.[95,112,113]

Approximately 200 to 300 mg per day of hydrocortisone is considered a physiologic stress dosage, such that dosage recommendations range from 50 to 100 mg IV every 6 to 8 hours. Another option is to administer a 50- to 100-mg bolus of hydrocortisone, followed by an infusion of 20 mg per hour.[95,96,112,113]

If the diagnosis of adrenal insufficiency is correct, these measures will improve the blood pressure and clinical picture over 4 to 6 hours. A careful search for a precipitating cause, especially infections, should have been completed by now and empirical antibiotic therapy often started. The rate of saline infusion and the dose of IV steroids can often be tapered after 24 hours. By the third or fourth day, conversion to oral hydrocortisone is feasible, usually at twice the maintenance dose (40 mg AM, 20 mg PM) initially, then to the standard replacement dose (20 mg AM, 10 mg PM). Hydrocortisone can be discontinued altogether if the random cortisol exceeds 25 µg/dL (preferably greater than 33 µg/dL) and the patient is much improved clinically. If there is any doubt, IV steroids should be continued until an ACTH stimulation test can be completed. Fludrocortisone, a mineralocorticoid, should be administered in a dose of 100 µg by mouth before cessation of the saline infusion, and it should be continued every 12 to 24 hours as maintenance.[95,96,112,113]

Chronic replacement therapy in patients with established adrenal insufficiency consists of hydrocortisone, 20 mg on arising and 10 mg at 6 PM, as well as fludrocortisones, 100 µg per day. During minor to moderate febrile illness or stress, the patient should be advised to increase the glucocorticoid dose two- or threefold for the few days of illness, but the fludrocortisone dose is not changed. For moderately stressful procedures like endoscopy or angiography, a single 100-mg IV dose of hydrocortisone is given prior to the procedure.[96]

KEY CONCEPTS

- Thyroid storm is a life-threatening decompensation of severe hyperthyroidism precipitated by an intercurrent illness, typically sepsis. The hallmarks of thyroid storm include hyperthermia, exaggerated tachycardia, altered mental status, and gastrointestinal symptoms. Therapy of thyroid storm includes actions to reduce production of thyroid hormone, to inhibit thyroid hormone release, to block peripheral conversion of T_4 to T_3, to initiate beta-adrenergic blockade, to institute general supportive measures, and to identify and treat the precipitating event.
- Myxedema coma is a life-threatening deterioration of severe chronic hypothyroidism precipitated by an acute intercurrent illness. The prototypical case is an elderly woman in the winter who presents with marked hypothermia, altered mental status, respiratory failure, and hypotension. The management of myxedema coma requires immediate attention to airway management, fluid resuscitation, thyroid hormone replacement, general supportive measures, and treatment of the precipitating illness.
- Hallmarks of chronic adrenal insufficiency include generalized weakness, malaise, fatigue, gastrointestinal symptoms, weight loss, blood pressure less than 110/70 mm Hg, and hyponatremia. Primary autoimmune adrenal failure is the more common cause and is distinguished by the presence of hyperpigmentation, hyperkalemia, and more severe orthostasis. Hypopituitarism resulting in secondary adrenal insufficiency is distinguished by more severe hypoglycemia and the lack of the classic features seen in primary disease.
- Hypotension refractory to fluid resuscitation may be the only clue to the diagnosis of adrenal crisis or relative adrenal insufficiency of critical illness. In this setting, a random serum cortisol level should be obtained and IV hydrocortisone administered before confirmation is obtained.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.