Thyroid dysfunction (hyperthyroidism and hypothyroidism) arguably represents the most common form of endocrine disorder. Together with adrenal insufficiency, these disease states are often manifested with protean symptoms, such as fatigue and weakness, making them a diagnostic challenge. In their advanced states, classic manifestations develop, rendering each disorder more recognizable. Each disorder is also capable of producing life-threatening symptoms when it is untreated or precipitated by other stressors. For patient outcomes to be improved, prompt recognition and therapeutic intervention are critical.

**HYPERTHYROIDISM**

**Perspective**

Background and Epidemiology

Hyperthyroidism is a condition caused by overproduction and increased circulation of thyroid hormone. The disorder runs the spectrum from subclinical hyperthyroidism to thyrotoxicosis, a life-threatening event. Thyrotoxicosis is a hypermetabolic condition that results from elevated levels of thyroid hormones (T₄ and T₃). This can occur from hormone overproduction (Graves’ disease, toxic multinodular goiter), increased thyroid hormone release from an injured gland (thyroiditis, trauma), or exogenous thyroid hormone (thyrotoxicosis factitia). For the purposes of this discussion, the terms hyperthyroidism and thyrotoxicosis are used interchangeably.

Recent work has estimated the incidence of thyrotoxicosis at 80/100,000 per year in women and 8/100,000 per year in men.¹ A population-based study in the United Kingdom demonstrated an incidence of 0.9/100,000 in children younger than 15 years. Most cases of thyrotoxicosis (>80%) are due to autoimmune disease.² The prevalence of hyperthyroidism is five to ten times less than that of hypothyroidism.

The myriad causes of thyrotoxicosis are listed in Box 128-1. Graves’ disease (diffuse toxic goiter) accounts for approximately 80% of all cases. Toxic multinodular goiter occurs most frequently in areas of iodine deficiency. It accounts for approximately 15% of thyrotoxicosis cases. In the United States, the incidence of toxic multinodular goiter is much lower than the global rate. Toxic adenoma is the third major cause of hyperthyroidism, accounting for approximately 3 to 5% of cases. Other less common causes of hyperthyroidism include thyroiditis (traumatic, infectious, or from radiation), ectopic thyroid tissue (lingual thyroid), tumors (pituitary, thyroid), drug induced (lithium, amiodarone), and exogenous thyroid hormone (from therapy or surreptitious consumption of thyroid hormone).³⁴

**Principles of Disease**

**Anatomy and Physiology**

The normal adult thyroid gland is a highly vascular organ overlying the anterior trachea. Its structure is bilobar with a median isthmus and total weight ranging from 10 to 30 g (Fig. 128-1). It receives its blood supply at a rate of 80 to 120 mL/min from the inferior and superior thyroid arteries, which are direct branches of the subclavian and external carotid arteries, respectively. The thyroid’s function is to secrete two iodinated hormones: triiodothyronine (T₃) and thyroxine (T₄). Only about 20% of circulating T₃ is directly secreted by the thyroid; the remainder is produced by peripheral conversion of T₄ to the more biologically active T₃. This process occurs predominantly in the liver and in skeletal muscle. The thyroid is the only endocrine gland that stores large quantities of hormone, with enough for about 100 days’ supply.

Regulation of hormone production is through a negative feedback loop involving the hypothalamic-pituitary-thyroid axis (Fig. 128-2). As the serum levels of T₄ and T₃ fall, the hypothalamus releases the tripeptide thyrotropin-releasing hormone (TRH), which in turn stimulates the anterior pituitary gland’s release of the polypeptide thyroid-stimulating hormone (TSH) from its thyrotroph cells. TSH then binds to epithelial cells on the thyroid gland, stimulating follicular cells to synthesize and secrete the thyroid hormones T₄ and T₃. TRH release may also result from exercise, stress, malnutrition, hypoglycemia, and sleep. The function of thyroid hormone is to influence the metabolism of cells by increasing their basal metabolic rate. It has a role in protein synthesis and function together with other hormones necessary for normal growth and development, such as human growth hormone and insulin.

**Pathophysiology**

T₃ is a prohormone with only mild intrinsic activity, whereas T₄ is the biologically active hormone. Typically, T₄ deiodination occurs at the outer ring of T₄, forming T₃. However, during systemic illness, deiodination occurs at an inner ring of T₄, resulting in reverse T₃, which is biologically inactive. More than 99.5% of thyroid hormones are protein bound in the serum to thyroxine-binding globulin (TBG) and other proteins, rendering them metabolically inactive. As a result, only free T₄ and free T₃ are clinically relevant.

Whereas iodide is a necessary substrate for thyroid hormone production, excess iodide can have two different effects. In the Wolff-Chaikoff effect, excess iodine inhibits iodide trapping, thyroglobulin iodination, and release of thyroid hormone from the
This inhibition is transient, typically lasting only a matter of days. Paradoxically, an iodide load can induce hyperthyroidism (Jod-Basedow effect) in some patients with multinodular goiter and occult Graves’ disease.

Thyroid hormone affects the metabolism of all tissues through varied mechanisms. It regulates gene activity by interaction at nuclear receptors and has direct effects on metabolism by interaction with cellular enzymes, like adenosine triphosphatase. Of note, T₃ and T₄ increase the expression and sensitivity of beta-adrenergic receptors, dramatically increasing response to endogenous catecholamines.

Graves’ Disease. In the United States, Graves’ disease is the most common form of hyperthyroidism. In this autoimmune disorder, autoantibodies are formed to the TSH receptor, where they bind
and stimulate the receptors. The overstimulated gland enlarges and increases thyroid hormone production and release. The triad of goiter, exophthalmos, and pretibial myxedema is diagnostic of Graves’ disease. The disease predominantly affects women and those with a family history of hyperthyroidism; it typically occurs between the ages of 20 and 40 years.

Toxic Multinodular Goiter. Toxic multinodular goiter is the second leading cause of hyperthyroidism in the United States. It is characterized by multiple autonomously functioning nodules developing in women older than 50 years. It is rare in youth, except in those with preexisting nontoxic multinodular goiters or living in iodine-deficient regions, such as Central America, South America, the Himalayas, eastern Europe, and central Africa. The hyperthyroidism in toxic multinodular goiter 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. Graves’ disease typically is manifested in the sixth decade of life; cardiovascular manifestations like atrial fibrillation and heart failure predominate, whereas tremors and hypermetabolic features are less pronounced. Muscle wasting and weakness are common, and the patient is often described as apathetic. Obstruction of the airway is a concern as multinodular goiters often extend retrosternally.

Toxic Adenoma. A toxic adenoma is commonly referred to as a hot nodule. This single hyperfunctioning nodule typically affects the same population as toxic multinodular goiter does, but it occurs less commonly.

Thyroiditis. Any inflammatory process that results in thyroid gland inflammation can lead to thyroiditis. The inciting process may be autoimmune, drug induced, infectious, or traumatic. Inflammation leads to follicular cell breakdown, with resultant release of preformed thyroid hormone, causing acute thyrotoxicosis. The most common form of thyroiditis in the United States is Hashimoto’s thyroiditis, an autoimmune disorder characterized by the presence of thyroid antibodies and lymphocytic infiltration of the thyroid gland. Typically, patients present with a painless goiter and hypothyroidism, but some have transient thyrotoxicosis (hashitoxicosis) that may last for a few months.

Postpartum and Sporadic Thyroiditis. Other autoimmune disorders of the thyroid include postpartum thyroiditis and sporadic thyroiditis. Referred to as painless, or silent, thyroiditis, they are typified by a small nontender goiter and mild symptoms. It is estimated that 5 to 10% of women have postpartum thyroiditis. The diagnostic triad consists of the lack of previous history of thyroid disorder, an abnormal TSH concentration during the first postpartum year, and the absence of TSH receptor antibodies (Graves’ or a toxic nodule. Classically, these patients present with thyrotoxicosis 6 weeks to 6 months postpartum, followed by a hypothyroid state lasting up to 6 months; a euthyroid state returns by the end of the first postpartum year. However, the majority of patients present with either hyperthyroidism alone or lone hypothyroidism. The recurrence rate in subsequent pregnancy is estimated at 69%, and some women have permanent hypothyroidism. Sporadic thyroiditis is indistinguishable from postpartum thyroiditis except that it is unrelated to pregnancy. It may account for up to 1% of thyrotoxicosis, and most patients recover; 20% have hypothyroidism.

Subacute Thyroiditis. Subacute thyroiditis (de Quervain’s thyroiditis) is thought to be caused by a viral infection of the thyroid, often appearing after an upper respiratory infection. However, a study was unable to detect viral titers in 852 patients with subacute thyroiditis. It is manifested with a typical viral syndrome prodrome (fatigue, myalgias, and pharyngitis), followed by fever and severe anterior neck pain. Pain may radiate to the jaw, ears, or occipital area. The thyroid is exquisitely tender, and pain can occur with head movement or swallowing. During the acute painful phase, a minority of patients have symptoms of hyperthyroidism (diaphoresis, palpitations, and tremor) lasting several weeks. Subacute thyroiditis may account for 2% of thyrotoxic patients; it occurs in the fourth and fifth decades of life and is more common in women than in men.

Suppurative Thyroiditis. Suppurative thyroiditis is a rare but potentially life-threatening infection of the thyroid. Patients present with fever and anterior neck pain, neck swelling, induration, and erythema as well as dysphonia and dysphagia. Infectious causes are overwhelmingly bacterial (aerobic and anaerobic) and very rarely parasitic, mycobacterial, or fungal. Most patients have preexisting thyroid disease and are immunocompromised (AIDS).

Drug-Induced Thyroiditis. Amiodarone contains a high amount of iodine (37%, about 400 times the daily requirement) and as a result can unmask hyperthyroidism in patients with multinodular goiter and subclinical Graves’ disease. More commonly, the cytotoxic effects of amiodarone destroy thyroid cells, resulting in a release of preformed hormone. An exacerbation of the tachyarrhythmia for which the patient is being treated 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. Mechanisms vary, but lithium reportedly induces sporadic thyroiditis by direct toxic effects.

Factitious Thyroiditis. Thyrotoxicosis factitia results from ingestion of thyroid hormone. Although this can be iatrogenic or the result of patient medication error, the majority of cases stem from medical personnel with psychiatric illness who surreptitiously self-administer the medication. Cases of factitious thyrotoxicosis have been reported worldwide as a result of the consumption of bovine thyroid hormone in contaminated beef and from adulterated weight loss products. By contrast, inadvertent acute ingestions of thyroid hormone usually manifest only minor toxicity. Whereas the dose plays a role, the 7-day half-life of T4 allows physiologic compensation, such as the suppression of T4 to T3 conversion, inhibition of endogenous hormone production by negative feedback loops, and downregulation of thyroid hormone receptors.

Clinical Features

Symptoms

The variable presentation of thyrotoxicosis among patients creates a diagnostic challenge (Box 128-2). Hyperthyroidism induces a hypermetabolic state and increases beta-adrenergic activity. The resulting clinical manifestations range from vague constitutional symptoms to more organ-specific symptoms. Thyroid storm, the most severe manifestation of the disease, is a life-threatening state that requires prompt intervention. Variables that affect the severity of disease include age, disease duration, hormone levels and rate of rise, drug interactions, and stress of concurrent illness. Hyperthyroidism in elders often is manifested in subtle ways, mimicking symptoms of aging or masquerading as diseases of the cardiovascular, gastrointestinal, or nervous system. Gradual or long-standing thyrotoxicosis can go unnoticed by the patient, or symptoms may be attributed to other causes like emotional stress, dieting, or physical deconditioning. The clinical manifestations do not necessarily correlate with the degree of biochemical abnormality.

Constitutional and hypermetabolic symptoms are common in thyrotoxicosis. These symptoms include fatigue, generalized
weakness, weight loss, heat intolerance, and increased perspiration. Weight loss averaging 15% of baseline can be seen despite increased calorie intake.

Common neuro-psychiatric symptoms include anxiety, nervousness, restlessness, tremor, akathisia (inability to sit still), insomnia, memory loss, and poor attention span. Patients are often emotionally labile and irritable. Altered mental status and coma may be seen in thyroid storm. Thyroid myopathy typically affects proximal muscle groups but can also lead to weakness of distal and bulbar muscles. Common presenting symptoms include myalgias, fatigue, and poor exercise tolerance. Patients often report difficulty in combing their hair, climbing stairs, or rising from a seated position. Thyroid myopathy leading to respiratory weakness may be manifested as dyspnea. In the extreme, this condition will require ventilatory support. Thyrotoxic periodic paralysis is manifested as a sudden and profound muscle weakness progressing to flaccid paralysis. It closely resembles familial hypokalemic periodic paralysis.

Palpitations, dyspnea on exertion, and reduced exercise tolerance are common cardiopulmonary complaints. Elders are more prone to cardiac manifestations and often present with new-onset angina, atrial fibrillation, or congestive heart failure as the only manifestations of thyroid disease. Superior vena cava syndrome and dyspnea can occur as a result of compression of vascular and tracheal structures by an enlarged thyroid gland.

An increase in the frequency of bowel movements is the most common gastrointestinal symptom. Dysphagia is also common and can be due to either compression of the esophagus by an enlarged thyroid gland or dysmotility related to thyrotoxic myopathy.

Thyrotoxicosis can cause reproductive endocrine dysfunction in both men and women. Changes in menses can range from amenorrhea to menometrorrhagia. As a result of the increase in estrogen, men may experience gynecomastia, decreased libido, and erectile dysfunction. Infertility related to hyperthyroidism may affect both sexes.

Graves’ ophthalmopathy commonly causes eyelid retraction, lid lag, proptosis, and staring eyes. Although these symptoms were previously thought to occur only with Graves’ disease, one author suggests that they are present in thyrotoxicosis in the absence of an autoimmune phenomenon, in children and adolescents. Graves’ ophthalmopathy is also associated with restrictive extraocular myopathy, exophthalmos, and, less commonly, optic nerve dysfunction. Patients often complain of irritation and excessive tearing as early symptoms; diplopia, retrobulbar discomfort, blurring of vision, and foreign body sensation occur late in the disease.
Thyroid Storm

Thyroid storm is a rare, life-threatening form of severe thyrotoxicosis. Although it can occur as the result of unrecognized or undertreated thyrotoxicosis, more often it is an acute reaction to thyroid or nonthyroid surgery, trauma, infection, iodine load (contrast media or amiodarone), or parturition in patients with preexisting hyperthyroidism. Other precipitants include acute myocardial infarction, pulmonary embolism, and diabetic ketoacidosis (Box 128-4). It affects 1 to 2% of patients with hyperthyroidism and up to 10% of hospitalized thyrotoxic patients. Untreated, mortality approaches 100%, but prompt recognition and aggressive therapy have lowered mortality to 20 to 30%.19 Nearly all cases are related to Graves’ disease or occasionally toxic multinodular goiter and toxic adenoma; it rarely occurs in other causes of thyrotoxicosis.

The typical clinical manifestations of hyperthyroidism are exaggerated in thyroid storm. Marked pyrexia to 104 to 106°F, tachycardia (often in excess of 140 beats/min), and altered mental status (agitation, delirium, or coma) are common features. These findings coupled with the clinical picture of a patient with hyperthyroidism, lid lag, stare, goiter, ophthalmopathy, and tremor should alert the clinician to the diagnosis. Cardiovascular collapse can result in congestive heart failure, hypotension, and cardiac arrhythmias. Hypotension can also result from volume depletion secondary to nausea, vomiting, and diarrhea. Abdominal pain is common; less commonly hepatic failure with cholestatic jaundice occurs, which is an indicator of a poor prognosis.20

Hyperthyroidism increases catecholamine receptor expression. As such, an exaggerated response is seen in the face of the adrenergic surge associated with physiologic stressors such as sepsis or trauma, yielding thyroid storm. The clinical picture that ensues should prompt the clinician to the diagnosis; however, no validated diagnostic system exists. Currently, the only tool available is a scoring system developed by Burch and Wartofsky, which can help distinguish between thyrotoxicosis, impending thyroid storm, and frank thyroid storm (Table 128-1).19

Diagnostic Strategies

The diagnosis of hyperthyroidism can be simplified into a two-step process. The initial diagnosis is based on the clinical picture coupled with confirmatory laboratory values. Once the diagnosis of hyperthyroidism is established, if the etiology is unclear, nuclear imaging with radioiodine is generally performed; this second step is a 24-hour test and thus not useful for the emergency physician but rather a tool for further evaluation once the diagnosis of thyrotoxicosis has been established.

Reliable assays for serum TSH and free T4 have made the laboratory diagnosis of hyperthyroidism straightforward. Measurement of serum TSH is the single best test to assess thyroid function. A normal TSH level excludes hyperthyroidism and an elevated TSH level is generally diagnostic for hypothyroidism. In thyrotoxicosis, serum TSH concentration is depressed or undetectable (values <0.05 μU/mL in third-generation assays). Values above this threshold associated with hyperthyroidism are consistent with subclinical disease.21 Assessment of thyroid function during acute nonthyroidal illness is difficult, especially in critically ill patients. Severe systemic illness depresses TSH production, leading to low levels of TSH, free T3, and free T4. Once referred to as the euthyroid sick syndrome, it appears to be a transient form of central hypothyroidism.22 It is considered an adaptive response during systemic stress to prevent excessive catabolism. Patients taking dopamine, glucocorticoids, somatostatin, and octreotide may also have depressed TSH levels but not to the degree of patients with hyperthyroidism.23 Measurement of thyroid hormone levels can help determine the degree of hyperthyroidism. Because nearly all T3 and T4 is bound to TBG, assays measuring total T3 and T4 are influenced by changes in TBG and are unreliable. Increases in TBG are seen in pregnancy,
Table 128-1 Diagnostic Criteria for Thyroid Storm

<table>
<thead>
<tr>
<th>Fever (°F)</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>99-99.9</td>
<td>5</td>
</tr>
<tr>
<td>100-100.9</td>
<td>10</td>
</tr>
<tr>
<td>101-101.9</td>
<td>15</td>
</tr>
<tr>
<td>102-102.9</td>
<td>20</td>
</tr>
<tr>
<td>103-103.9</td>
<td>25</td>
</tr>
<tr>
<td>≥104</td>
<td>30</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tachycardia (beats/min)</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-109</td>
<td>5</td>
</tr>
<tr>
<td>110-119</td>
<td>10</td>
</tr>
<tr>
<td>120-129</td>
<td>15</td>
</tr>
<tr>
<td>130-139</td>
<td>20</td>
</tr>
<tr>
<td>≥140</td>
<td>25</td>
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<table>
<thead>
<tr>
<th>Mental Status</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Mild agitation</td>
<td>10</td>
</tr>
<tr>
<td>Delirium, psychosis</td>
<td></td>
</tr>
<tr>
<td>Extreme lethargy</td>
<td>20</td>
</tr>
<tr>
<td>Coma, seizures</td>
<td>30</td>
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</table>

<table>
<thead>
<tr>
<th>Congestive Heart Failure</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Mild (edema)</td>
<td>5</td>
</tr>
<tr>
<td>Moderate (rales)</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>15</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Gastrointestinal and Hepatic Symptoms</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, abdominal pain</td>
<td>10</td>
</tr>
<tr>
<td>Unexplained jaundice</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Precipitating Event</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>10</td>
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</tbody>
</table>


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

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Elevation of free T₄ and free T₃ in conjunction with TSH suppression is diagnostic of thyrotoxicosis. Subclinical hyperthyroidism is likely if TSH is suppressed and free T₄ is normal. T₃ toxicosis occurs in about 5% of patients with thyrotoxicosis, more commonly in toxic multinodular goiter. These patients have an elevated free T₃ level and a normal free T₄ level. When the reverse pattern is present (normal free T₃ level and elevated free T₄ level), the differential includes thyroiditis, exogenous levothyroxine ingestion, and hyperthyroidism in the elderly, often with suppressed T₄ to T₃ conversion due to comorbid illness (Table 128-2).

Additional laboratory abnormalities may be seen in thyrotoxicosis and thyroid storm. Nearly 50% of thyrotoxic patients have hyperglycemia. This is likely to be the result of increased glycogenolysis and catecholamine-mediated antagonism of insulin. Mild hypercalcemia, seen in 10% of patients, is related to hormone-mediated bone resorption and associated with osteoporosis and increased fracture risk.

The results of liver function tests are frequently abnormal in thyrotoxic patients. Mild increases in serum aspartate transaminase, alanine transaminase, lactate dehydrogenase, bilirubin, and alkaline phosphatase may be seen. The elevations in serum bilirubin do not typically result in clinical jaundice. Other frequent laboratory abnormalities include leukocytosis with a leftward shift, mild normocytic normochromic anemia, and low serum cholesterol levels.²¹

In thyroiditis, the diagnostic evaluation is more difficult. An exquisitely tender gland and an erythrocyte sedimentation rate above 100 mm/hr make the diagnosis of subacute thyroiditis likely. The other forms of thyroiditis lack these findings. Doppler ultrasound examination of the thyroid may be helpful in differentiating among the various causes of thyrotoxicosis. A hypervascular enlarged gland is seen in Graves’ disease, nodules in toxic multinodular goiter, and decreased Doppler flow in thyroiditis or factitious thyrotoxicosis.²⁴ If factitious thyrotoxicosis is suspected, low thyroglobulin levels may confirm the diagnosis as these levels are elevated in all other forms of thyrotoxicosis. Furthermore, radioactive iodine uptake is depressed in thyroiditis and factitious thyrotoxicosis but increased in hyperthyroidism.

**Differential Considerations**

Because of the protean symptoms of hyperthyroidism, the differential diagnosis for the thyrotoxic patient is broad. An anxious patient may be interpreted to be manic or experiencing a panic attack. The hyperadrenergic state may be confused with that seen...
in patients with sympathomimetic (cocaine or amphetamine) intoxication, suffering from anticholinergic crisis, or experiencing withdrawal from alcohol or sedative-hypnotics.

The hyperpyrexia and altered mental status seen in thyroid storm may mimic other hyperthermic disorders such as heatstroke, neuroleptic malignant syndrome, serotonin syndrome, bacterial meningitis, and sepsis.

Elders often present with apathetic hyperthyroidism, which lacks the hyperadrenergic features of thyrotoxicosis but is associated with blunted facial expressions and an altered mental status. This is commonly seen in patients older than 70 years with multinodular goiter and can be confused with psychiatric illness. In addition, these patients also present with new-onset atrial fibrillation and congestive heart failure. The elderly are also more prone to hyperthyroidism-induced weight loss, leading to a search for an occult malignant neoplasm.

**Management**

Management of thyrotoxicosis is based on symptom severity. For those with mild symptoms, outpatient referral and management are appropriate. Patients with moderate to severe symptoms are best managed in the emergency department (ED) setting. Treatment is divided into supportive, symptomatic, and thyroid directed (Box 128-5). In addition, it is important to identify and to treat the precipitating cause of thyroid storm.

**Supportive Treatment**

Supportive therapy for thyroid storm patients includes aggressive management of hyperthermia with cooling and acetaminophen; aspirin is avoided in thyrotoxic patients as it decreases protein management of hyperthermia with cooling and acetaminophen; Supportive therapy for thyroid storm patients includes aggressive fluids for hypotension, regardless of the agent used, because thyrotoxicosis can lower systemic vascular resistance and cause congestive heart failure. In patients with low ejection fraction on echocardiography, angiotensin-converting enzyme inhibitors, diuretics, and digoxin are appropriate alternatives. Atrial fibrillation is often refractory to rate control until antithyroid therapy is administered.

**Box 128-5 Management of Thyroid Storm**

<table>
<thead>
<tr>
<th>Beta-adrenergic Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol 60-80 mg PO every 4 hr</td>
</tr>
<tr>
<td>or Metoprolol 50 mg PO every 6-12 hr</td>
</tr>
<tr>
<td>If IV route is required: propranolol 0.5-1.0 mg IV slow push test dose, then repeat every 15 min to desired effect, then 1-2 mg every 3 hr</td>
</tr>
<tr>
<td>or Esmolol 250-500 µg/kg bolus, then 50-100 µg/kg/min infusion</td>
</tr>
<tr>
<td>Strict contraindication to beta-blocker: reserpine 2.5-5 mg IM every 4 hr</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibition of Thyroid Hormone Synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylthiouracil 600-1000 mg loading dose, then 300 mg every 6 hr (maximum daily dose, 1200 mg)</td>
</tr>
<tr>
<td>or Methimazole 20-30 mg initially, then 20-30 mg every 6 hr (maximum daily dose, 120 mg)</td>
</tr>
<tr>
<td>(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.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibition of Thyroid Hormone Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated solution of potassium iodide (SSKI) 5 gtt by mouth, NG, or PR every 6 hr</td>
</tr>
<tr>
<td>or Lugol’s solution 4-8 gtt by mouth, NG, or PR every 6 hr</td>
</tr>
</tbody>
</table>

| 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 |

**Administration of Corticosteroids (inhibit T₄ to T₃ conversion, treat relative adrenal insufficiency)**

Hydrocortisone 100 mg IV, followed by 100 mg every 8 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/v/0.9 NS 125-1000 mL/hr depending on volume status and CHF

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 (blocks enterohepatic recirculation of thyroid hormone), 4 g PO every 6 hr

CHF: congestive heart failure; D/v/0.9 NS, 5% dextrose in 0.9% normal saline; IV, intravenously; NG, by nasogastric tube; PO, by mouth; PR, in rectum; T₄, triiodothyronine; T₃, thyroxine.
Thyroid-Directed Treatment

Thyroid-directed therapy has three goals: to reduce thyroid hormone production, to prevent thyroid hormone release, and to block peripheral conversion of T4 to T3. Although it is not a specific goal, an additional goal is the avoidance of therapeutic interventions that may worsen thyrotoxicosis. As such, certain drugs should be avoided in the thyrotrophic patient. Amiodarone and iodinated contrast material both contain iodine and can increase thyroid hormone production. Aspirin can increase free thyroid hormone concentrations through its effect on protein binding. Finally, pseudoephedrine, ketamine, and albuterol should be used cautiously as they increase sympathetic tone and can exacerbate the adrenergic effects of thyrotoxicosis.

Reducing Thyroid Hormone Production. Thionamides inhibit oxidation and organic binding of iodine to thyroglobulin, thereby blocking synthesis of thyroid hormone. Either propylthiouracil (PTU) or methimazole can be used. PTU has the additional effect of impairing conversion of T4 to T3; methimazole has a longer duration of action. PTU is given as an initial loading dose of 600 to 1000 mg by mouth, followed by 300 mg every 6 hours, to a maximum daily dose of 1200 mg.25 The recommended dose for methimazole is 20 to 30 mg initially, with the same dose repeated every 4 hours to a maximum daily dose of 120 mg.27 Both PTU and methimazole may be given by nasogastric tube or by retention enema as needed.28 There are no intravenous forms of PTU or methimazole; although intravenous administration of methimazole has been attempted, this should be considered only as a last resort.

Inhibiting Thyroid Hormone Release. Despite the blockade of thyroid hormone synthesis by thionamides, release of preformed hormone in the gland is still a concern. Inorganic iodine blocks the release of stored thyroid hormone. However, an iodine load can increase the synthesis of thyroid hormone, so these agents should not be administered until 1 hour after the initiation of PTU or methimazole therapy. Traditionally, oral iodine in the form of potassium iodide (SSKI) 5 gtt every 6 hours or Lugol’s solution 4 to 8 gtt every 4 to 6 hours is administered. Like the thionamides, these agents may be given by nasogastric tube or by retention enema as needed. Lithium may be considered an alternative therapy for iodine-allergic patients. The lithium dose is 300 mg every 6 to 8 hours orally to obtain a lithium serum concentration of 0.6 to 1.0 mEq/L.27 Lithium is also the agent of choice for iodine-induced hyperthyroidism, which is usually the result of the administration of amiodarone or iodinated contrast material.

Side effects of thionamide therapy range from mild to life-threatening. Mild reactions (urticaria or macular rash, arthralgia, and gastrointestinal upset) occur in up to 5% of patients receiving methimazole or PTU. Side effects are dose related for methimazole but not for PTU. Life-threatening side effects are associated with ongoing therapy and occur within the first 90 days of treatment. Agranulocytosis can occur with either drug and should prompt drug discontinuation. PTU-induced hepatotoxicity has earned the drug a black box warning from the Food and Drug Administration. Finally, polyarthritis and vasculitis (drug-induced lupus) can occur; vasculitis is associated with PTU more than with methimazole.

Inhibiting Conversion of T4 to T3. Corticosteroids are capable of both inhibiting peripheral conversion of T4 to T3 and blocking the release of hormone from the thyroid gland. When steroids are used in conjunction with PTU and iodide, the concentration of T3 can return to normal within 48 hours. In addition, corticosteroids will treat adrenal insufficiency that can occur concomitantly with thyroid storm. Adrenal insufficiency is usually due to increased clearance of cortisol in thyroid storm and the increased demand for cortisol in these critically ill patients. Hydrocortisone can be administered as an initial bolus of 100 mg IV, then 100 mg every 8 hours for several days. Dexamethasone can also be used in doses of 2 to 4 mg IV.

Miscellaneous Therapies

Cholestyramine, an anion exchange resin, interrupts the enterohepatic recirculation of thyroid hormone by binding it in the bowel lumen. Although it has been shown to result in a more rapid decline in hormone levels compared with thionamides alone, it requires weeks of therapy and as such is reserved for outpatient management.29 Plasmapheresis, plasma exchange, and dialysis have been used in thyroid storm. They represent an attempt at extracorporeal removal of circulating thyroid hormone. Whereas the literature is split on the benefit of these modalities, plasmapheresis demonstrates the greatest putative benefit and can be initiated when a patient with thyroid storm demonstrates deterioration despite aggressive therapy.

L-Carnitine, given 1 g orally every 12 hours, has been used in thyroid storm. Theoretically, it inhibits entry of thyroid hormone into cell nuclei.30 Neither radioactive iodine nor surgery plays a role in the management of thyroid storm or thyrotoxicosis until a sustained euthyroid state has been established because these interventions can precipitate storm.31

Treatment of subacute thyroiditis generally involves only nonsteroidal anti-inflammatories to control pain. Prednisone is used for refractory cases. Only a minority of patients have thyrotoxicosis, which is typically mild and requires no additional treatment beyond beta-blockers. The same holds true for thyrotoxicosis from exogenous thyroid hormone ingestion. In this situation, the thyroid gland has stopped production from negative feedback, so thionamides and iodine are ineffective. Management of drug-induced hyperthyroidism involves removal of the offending agent (amiodarone, lithium) and symptomatic treatment as needed (Box 128-6).

**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 128-5)
  - ACEI, digoxin, diuretics as needed
- If depressed ejection fraction
  - Avoid beta-blocker or ¼ dose
  - ACEI if blood pressure adequate
  - Digoxin and furosemide as needed
- If pulmonary hypertension
  - Oxygen
  - Sildenafil

**Atrial Fibrillation**
- Beta-blocker preferred for rate control (dose as in Box 128-5)
- Calcium channel blockers prone to hypotension; diltiazem 10-mg test dose. Avoid verapamil.
- Digoxin less effective but may be tried
- Amiodarone should be avoided because of iodine load
- Refractory to conversion to sinus rhythm 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; NSAIDs, nonsteroidal anti-inflammatory drugs; PTU, propylthiouracil.
Identification and Treatment of the Precipitating Event

Thyroid storm is often precipitated by a physiologic stressor. It is critical to identify the cause to maximize therapeutic benefit. Infections are the most common precipitant. Chest radiography, urinalysis, and blood cultures are part of the routine evaluation. Empirical antibiotics are not recommended without an identified source of infection. Other common stressors include myocardial ischemia, pulmonary embolism, and stroke.

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 thyroid storm are candidates for an intensive care unit (ICU) admission. Interruption in therapy should be avoided because it can lead to a sudden recrudescence of symptoms and death.

Disposition and Consultation

Disposition is guided by symptom severity, with ICU admission for patients in thyroid storm. Patients with mild thyrotoxicosis (tremor, tachycardia, nervousness) controlled with first-line medication who are otherwise stable can be managed as outpatients. Admission to the hospital may be appropriate for patients who require more than beta-blockers for symptom control or whose symptoms persist despite therapy. Patients with rapid atrial fibrillation should be admitted to a monitored setting.

Patients managed as outpatients can be sent to a primary care physician or referred to an endocrinologist as appropriate.

**HYPOTHYROIDISM**

**Perspective**

**Background and Epidemiology**

Hypothyroidism is a condition in which the thyroid gland fails to produce or to secrete sufficient circulating thyroid hormone to meet the needs of the peripheral tissues. The condition results from either lack of stimulation of the thyroid gland (central or secondary hypothyroidism) or intrinsic gland dysfunction limiting hormone production (primary hypothyroidism). Hypothyroidism is the most common functional disorder of the thyroid gland.32

Hypothyroidism is a relatively common disorder of endocrine dysfunction with an annual incidence affecting approximately 80/100,000 men and 350/100,000 women.1 Thyroid disorders are the second most common endocrine condition after diabetes mellitus. Higher incidence rates are found in women than in men for all types of autoimmune disorders; the genetic disparity of thyroid diseases, such as diabetes mellitus, pernicious anemia, Addison's disease, and hyperparathyroidism.

Hashimoto's thyroiditis or chronic autoimmune lymphocytic thyroiditis, first described in 1912 by Hakaru Hashimoto, is one of the most common organ-specific autoimmune diseases and the most common cause of primary hypothyroidism. It is characterized by infiltration of the thyroid gland by lymphocytic inflammatory cells, which is then often followed by hypothyroidism as a result of destruction and eventual fibrous replacement of the gland's follicular tissue. Hashimoto's thyroiditis is the third most common autoimmune disease in the United States and the most frequent cause of hypothyroidism in adults. A systematic review of the literature estimates the annual incidence of Hashimoto's or autoimmune thyroiditis to be 80/100,000 per year (men) and 350/100,000 per year (women).1

Neonatal hypothyroidism results from decreased T4 production in the newborn and is the most preventable cause of intellectual disability.34 Most infants with congenital hypothyroidism have thyroid dysgenesis, which includes thyroid agenesis, thyroid hypogenesis, and a defect in thyroid migration leading to ectopic
thyroid tissue most commonly found at the base of the tongue (lingual thyroid). With thyroid dysgenesis, the thyroid tissue, if any, has insufficient function to sustain normal thyroid hormone production. In some cases of a lingual thyroid, patients may have local symptoms of dysphagia, dysphonia, hemorrhage, or upper airway obstruction decades later in life. The longer the diagnosis and treatment of congenital hypothyroidism are delayed, the greater the cognitive deficit will be compared with expected normals.

Previous treatment of hyperthyroidism may lead to iatrogenically induced hypothyroidism as a result of surgical thyroidectomy or radioactive iodine ablation therapy.

Lithium and amiodarone are well-known causes of hypothyroidism. Lithium, commonly prescribed for the treatment of bipolar disorder, has a side effect profile that includes goiter in up to 40% and hypothyroidism in about 20% of patients. The most relevant clinical action of lithium on the thyroid is the inhibition of T4 to T3 release. Lithium also increases thyroid autoimmunity if it is present before the initiation of lithium treatment. Treatment with exogenous thyroid hormone is effective and lithium therapy need not be discontinued.

Amiodarone is a class III antiarrhythmic medication that has a chemical structure similar to that of T4 and contains large amounts of iodine. As such, it inhibits the peripheral conversion of T4 to T3, leading to hypothyroidism. In addition, amiodarone is directly cytotoxic to the thyroid, has the intrinsic effect of blocking thyroid hormone entry into cells, and decreases T3 receptor binding. If amiodarone therapy must be continued for arrhythmia control, patients with amiodarone-induced hypothyroidism may be successfully treated with exogenous thyroid hormone replacement. Screening for thyroid dysfunction is recommended before initiation of therapy and during treatment with these medications.

Tyrosine kinase inhibitors are used as chemotherapeutic agents in the treatment of several types of malignant neoplasms, including thyroid cancer. Some medications in this class have been noted to profoundly alter thyroid function with enough frequency to warrant routine monitoring of thyroid function during treatment.

Insufficient dietary iodine intake leads to reduced T4 and T3 production. Although it is uncommon in developed nations, this is still a major concern in areas where the iodine content in the water is low. The compensatory increase in TSH concentration over time results in proliferation of gland cells and enlargement of the gland with a resultant goiter.

Thyroid physiology is altered during pregnancy, when increased circulating estrogen results in a 100 to 150% increase in TBG, which lowers free T4 levels. Human chorionic gonadotropin (hCG) and TSH have identical subunits, which then both stimulate the release of T4 and T3, resulting in a decreased level of TSH. Insufficient dietary iodine intake leads to reduced T4 and T3 production. Although it is uncommon in developed nations, this is still a major concern in areas where the iodine content in the water is low. The compensatory increase in TSH concentration over time results in proliferation of gland cells and enlargement of the gland with a resultant goiter.

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Signs and symptoms of hypothyroidism range from asymptomatic to overt organ failure that may lead to death (Box 128-8). Patients with early hypothyroidism often present with vague complaints. As such, clinicians should consider thyroid dysfunction in patients with generalized arthralgias, infertility or menstrual changes, depression, and hypercholesterolemia.

Typical symptoms develop insidiously and include fatigue, weakness, slowing of physical activity, constipation, heavier menstruation, alopecia and brittle hair, weight gain, intolerance to cold, goiter, hypertension, bradycardia, and facial edema. Skin may be dry, coarse, and pale from fluid accumulation and decreased circulation. Paresthesias of hands mimicking carpal tunnel have been described.

As the disease progresses, symptoms may include altered or decreased taste, hoarseness, edema of the hands and feet, slow speech, thickening of the skin, and thinning of the lateral third of the eyebrows. Patients with subclinical hypothyroidism may present with varying nonspecific signs and symptoms similar to those of patients with overt hypothyroidism but less pronounced.

Subclinical hypothyroidism progresses to clinical hypothyroidism at a rate of 5 to 18% per year in those with elevated TSH levels and detectable thyroid antibodies. Progression may be predicted by the degree of TSH elevation and appears more likely in patients with detectable serum antithyroid antibodies.

Hypothyroidism is responsible for multisystem organ disease. Even mild thyroid failure is a significant risk factor for the development of arterial stiffness from impaired endothelial function and artery intima-media wall thickening. Arterial stiffness is
Subclinical hypothyroidism is associated with lipid abnormalities; study outcomes vary, there is growing evidence to indicate that thyroid hormones may reflect the absence of the vasodilatory effects of T₃ on vascular pressure regulation and resultant hypertension. Vasoconstriction may be additional links between hypothyroidism and impaired blood vascular resistance and low cardiac output have been suggested to function, and systemic vascular resistance. Increased peripheral including its influence on cardiac contractility, heart rate, diastolic function, and systemic vascular resistance. Increased peripheral vascular resistance and low cardiac output have been suggested to be additional links between hypothyroidism and impaired blood pressure regulation and resultant hypertension. Vasoconstriction may reflect the absence of the vasodilatory effects of T₃ on vascular smooth muscle. Antihypertensive medications are usually ineffective in noneuthyroid individuals. Hemodynamic effects of subclinical hypothyroidism included impaired left ventricular function with lowered cardiac output and increased peripheral vascular resistance.

The accelerated atherosclerosis in hypothyroidism is ascribed to dyslipidemia, diastolic hypertension, and impaired endothelial function. There is a higher incidence of myocardial infarction in women with subclinical hypothyroidism compared with euthyroid controls; lipid profile abnormalities improve with the treatment of hypothyroidism. In addition, T₃ increases production and secretion of renin. In patients who are hypothyroid, renin levels are found to be low, which plays an important role in the acceleration of atherogenesis.

Subclinical hypothyroidism has been linked to alterations in cerebral perfusion and nerve conduction. Although neuropsychological dysfunction is not easily detected, working memory may become impaired. The Framingham study noted an increased risk of Alzheimer’s disease especially in women with subclinical hypothyroidism. Pulmonary abnormalities in hypothyroidism are primarily related to hypoventilation and hypercapnia. Between 35 and 65%
of patients with pulmonary hypertension have concomitant thyroid dysfunction. Although pulmonary artery pressures normalize after treatment of the thyroid disease, the exact relationship is not known. Because both diseases are associated with autoimmune disorders, they may share a common autoimmune pathophysiologic mechanism.

Changes in skin and hair characteristics may provide an early signal to dysfunction of thyroid hormone production. Cutaneous symptoms found in adults with hypothyroidism include cold, pale, and coarse skin often involving the extensor surfaces. Facial changes include periorbital edema, broadened nose, swollen lips, macroglossia, and flat facial expression. Body and scalp hair is brittle and coarse with a high rate of at least some degree of alopecia.

In pregnancy, hypothyroidism may be manifested classically, but it is often subtle and difficult to distinguish from normal changes in pregnancy. The secretion of hCG is greatest in the first trimester of pregnancy and plateaus in the second; hCG has inherent TSH-like activity and results in elevated T3 and T4 levels and increased TSH levels. The fetus begins to produce TSH toward the end of the first trimester; before this time the fetus relies on maternal TSH production. Normal maternal thyroid hormone production is therefore critical to fetal development.

In children, hypothyroidism may affect growth, development, and cognitive capacity. Declining growth velocity noticed during several years might be the first prompt to evaluate for thyroid disorders. This is secondary to retarded skeletal development and growth arrest from epiphyseal dysgenesis. T4 replacement will induce a rapid growth spurt, although predicted bone maturation size might not be achieved. The resultant height deficit is related to the delay in thyroid hormone replacement. In adults, thyroid hormone functions to regulate and to maintain bone mass. The duration of bone remodeling cycles is increased, with the osteoclastic resorption phase extended twofold and the osteoblastic phase extended fourfold. There is lower bone mass. The duration of bone remodeling cycles is increased, with a range of severe mental disorders from depression to severe cognitive impairment.

Diagnostic Strategies

Laboratory studies are used to confirm the diagnosis of hypothyroidism. Determination of an elevated TSH level is considered to be the most sensitive and single best screening test to confirm the diagnosis of primary hypothyroidism. TSH levels peak in the evening and are at their lowest in the afternoon but are also affected by physiologic conditions such as physical stress, illness, trauma, and malnutrition.

Myxedema Coma

Myxedema coma is the most severe manifestation of hypothyroidism. It is a life-threatening event that is most often precipitated by some stressful occurrence in patients with untreated or undertreated hypothyroidism. Precipitating events may include myocardial infarction, infection, sepsis, stroke, pulmonary embolus, prolonged exposure to cold, or exposure to drugs that suppress the central nervous system (Box 128-9). Patients with myxedema coma have a temperature below 37°C (98.6°F) in 15% of cases, whereas 15% of those patients have a temperature below 29.5°C (85°F). Diagnosis must often be made on the basis of clinical findings (Box 128-10). Treatment of myxedema coma requires potentially toxic doses of thyroid hormone, and mortality rates are high even with optimum therapy; without treatment, the mortality of this condition approaches 100%. Myxedema is associated with a range of severe mental disorders from depression to severe psychoses, sometimes called myxedema madness.

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**Box 128-9 Myxedema Coma: Aggravating or Precipitating Factors**

- Infection, sepsis (especially pneumonia)
- Exposure to cold
- Cerebrovascular accident
- Drug effect
  - Altered sensorium: sedative-hypnotics, narcotics, anesthesia, neuroleptics
  - Decreased T4 and T3 release: amiodarone, lithium, iodides
  - Enhanced elimination of T4 and T3: phenytoin, 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

**Box 128-10 Recognition of Myxedema Coma**

- Patient profile: elderly female in the winter
- Known hypothyroidism; thyroidectomy scar
- Hypothermia: temperature usually below 95.9°F; below 90°F is a poor prognostic sign; as low as 75°F reported; nearly 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 hypercapnia 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

TSH measurements may be unreliable in severely ill patients. An elevated TSH level with a low T4 level is indicative of primary hypothyroidism, and a low TSH level with a low T4 level is associated with central hypothyroidism. The T3 resin uptake index (T3 uptake × total serum T4 concentration) is also low. Increased TSH concentration with a normal T4 level represents subclinical hypothyroidism (Table 128-3). If the TSH level is normal but the T4 level is low, hypothyroxinemia exists; patients are often asymptomatic, but studies have found that patients with this degree of thyroid dysfunction do experience pathologic effects. The state of subclinical hypothyroidism may frequently progress to overt hypothyroidism in many patients.

A useful confirmatory test is the presence of thyroid antibodies (antithyroglobulin, antimicrosomal). They may help determine the etiology of hypothyroidism or may serve to predict future occurrence. Other laboratory findings may include mild anemia, hypercholesterolemia, elevated hepatic enzymes, elevated prolactin, and hyponatremia secondary to extracellular volume expansion produced by elevated antidiuretic hormone. Blood glucose
levels may be normal or low as a result of decreased gluconeogenesis and reduced insulin clearance.

The electrocardiogram is nonspecific in hypothyroidism. It might reveal sinus bradycardia with low-voltage complexes and nonspecific ST-T wave changes.

Imaging studies of the thyroid may detect infiltrative disease but are of limited use in hypothyroidism. Fine-needle biopsy of thyroid nodules is recommended. Radioactive iodine uptake and thyroid scanning are not helpful in hypothyroidism. Fine-needle biopsy of the thyroid nodules is recommended. Radioactive iodine uptake and thyroid scanning are not helpful in hypothyroidism because they require a functioning thyroid gland to provide diagnostic information.

**Differential Considerations**

Differential considerations include other causes of the common clinical presentations of hypothyroidism: congestive heart failure, pulmonary edema, depression, encephalopathy, hypothermia, systemic infection, and shock.

**Management**

**Hypothyroidism**

Replacement with levothyroxine (T4) remains the treatment of choice and resolves most physical and psychological signs and symptoms in most patients. Synthetic levothyroxine is a levo isomer of thyroxine and has activity identical to that of the endogenous hormone. Approximately 80% is absorbed from the gastrointestinal tract, predominantly in the small intestine. T4 levels peak approximately 2 to 4 hours after ingestion and remain therapeutic for up to 6 hours. T3 concentration rises more slowly because it is dependent on conversion from T4. Dose optimization is guided by monitoring of serum T4 and TSH levels. Patients with normally functioning thyroid glands require an iodine intake of 150 µg/day.

Levothyroxine is the drug of choice for patients with subclinical hypothyroidism and a serum TSH concentration above 10 mIU/L and for patients with a serum TSH concentration between 5.1 and 10.0 mIU/L in whom the decision to treat has been made. The usual daily dose is between 50 and 75 µg. The serum TSH concentration should be checked at 6- to 8-week intervals after initiation of treatment, and once a normal TSH level has been established, the TSH level should be rechecked at 6 months and then annually. In all cases, TSH concentration should be used as the guide to thyroid hormone replacement. Levothyroxine taken at bedtime has been shown to significantly improve TSH levels; however, quality-of-life variables have not been changed.

Studies comparing combination therapy of levothyroxine (T4) and T3 (triiodothyronine; Cytomel) with levothyroxine monotherapy alone have not established a significant benefit. However, some reports from combination therapy groups show improvement in depression and anxiety rating scales and lipid profiles but also show increased bone turnover.33

**Myxedema Coma**

The cornerstone for treatment of myxedema coma is rapid replacement of intravenous thyroid hormones T4 and T3 (Box 128-11). In elders and patients with cardiac comorbidities, T4 may be given as an initial bolus of 300 to 500 µg or as a split bolus of 200 to 300 µg 24 hours apart. Either initial dose is followed by 50 to 100 µg IV daily until the patient can take oral medications. In younger patients or those without cardiac risk factors, T4 may be administered at an initial dose of 10 to 20 µg IV followed by 10 µg IV every hour for 24 hours, then 10 µg IV every 6 hours for 1 or 2 days. Aggressive thyroid hormone replacement, support of vital functions, and treatment of the precipitating event are necessary. Stress doses of an intravenous glucocorticoid are recommended as there may be concomitant adrenal insufficiency. Hydrocortisone 50 to 100 mg IV every 6-8 hr is the drug of choice as it has both mineralocorticoid and glucocorticoid effects.

Hypotension may respond to crystalloid infusion, but vasopressors are occasionally required. In patients with initially refractory hypotension, the mere replacement of thyroid hormone may have a beneficial effect on improvement of blood pressure.

Passive rewarming with blankets and removal from the cold are generally sufficient. However, hemodynamically unstable patients with profound hypothermia require active rewarming.

Hyponatremia is largely due to free water retention and should be treated initially with water restriction. Hypertonic saline is indicated in patients with sodium levels below 120 mEq/L or if hyponatremia-induced seizures occur.

Metabolism of sedatives, narcotics, and anesthetics may be slowed, prolonging their effects. Therefore, lower dosages should be considered to prevent untoward effects of these medications, further complicating patient management.
Disposition

Most patients with hypothyroidism may be treated on an outpatient basis. Patients with severe hypothyroidism who require aggressive management or patients with myxedema coma require inpatient care, often in an ICU setting. Overly aggressive replacement of thyroid hormone may precipitate symptoms of hyperthyroidism or, rarely, thyroid storm, which also may require hospital admission.

ADRENAL INSUFFICIENCY

Perspective

Adrenal insufficiency, first described in 1855 by Thomas Addison, remains a potentially life-threatening disease. The clinical manifestations of deficient action or production of glucocorticoids are the result of either primary adrenal failure or secondary adrenal disease from malfunction of the hypothalamic-pituitary-adrenal (HPA) axis in its production of adrenocorticotropic hormone (ACTH). No matter what the etiology, the predominant symptoms are fatigue, generalized weakness, weight loss, and nonspecific gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain. Acute manifestations of disease may result in severe and possibly refractory hypotension.

The estimated prevalence of primary adrenal insufficiency is around 1/10,000 population. Secondary adrenal insufficiency has double the prevalence of primary adrenal insufficiency; the most common cause is exogenous corticosteroid administration.

Principles of Disease

Anatomy and Physiology

The adrenal glands are paired structures that sit in the retroperitoneum, one atop each kidney. They are found at the level of the twelfth thoracic vertebra, and each gland weighs about 4 g. The adrenal gland has two distinct structures, the adrenal cortex and the medulla, which are responsible for the release of the hormone aldosterone, corticosteroids, and catecholamines. The medulla acts in concert with the central nervous system to produce and to secrete the hormones epinephrine and norepinephrine in response to sympathetic stimulation. Anatomically, the adrenal cortex has three distinct zones: the zona glomerulosa, zona fasciculata, and zona reticularis. Functionally, the gland has two regions: the outer cortex, which includes the zona glomerulosa that secretes the mineralocorticoid aldosterone, and the inner medulla, which is composed of the zona fasciculata and zona reticularis that secrete, respectively, the mineralocorticoid cortisol and androgens or sex steroids.

ACTH produced and secreted by the anterior pituitary stimulates the adrenal cortex to predominantly synthesize and produce cortisol, which regulates carbohydrate, protein, and lipid metabolism, and aldosterone, which regulates fluid and electrolyte balance through sodium and potassium homeostasis. Cortisol is the primary glucocorticoid in humans, accounting for approximately 95% of all glucocorticoid activity; it is produced in quantities of about 10 mg/day, which is equivalent to 20 to 30 mg/day of hydrocortisone.

Pathophysiology

Primary adrenal insufficiency, or Addison’s disease, is the failure of the adrenal gland to produce cortisol, aldosterone, or both with an intact HPA axis (Fig. 128-3). In developed countries it is most commonly a result of autoimmune destruction. Adrenal insufficiency may occur alone, with other autoimmune diseases (polyglandular autoimmune syndrome type 2 and polygenic inheritance), or with hypoparathyroidism and mucocutaneous candidiasis (polyglandular autoimmune syndrome type 1) due to autosomal recessive inheritance of mutations in the autoimmune regulator (AIRE) gene 6. In primary disease, the HPA axis remains intact. Primary adrenal insufficiency is characterized by absent or low cortisol with high levels of circulating ACTH because of reduced negative feedback effects on the anterior pituitary. The increased ACTH concentration results in secretion of other hormones with similar chemical structure. One classic feature exemplifying this relationship is ACTH stimulation of melanocyte-stimulating hormone, which causes melanocytes to form a black pigment and the characteristic skin hyperpigmentation seen in primary adrenal insufficiency.

Secondary adrenal insufficiency is a result of impaired stimulation of the adrenals from disruption of normal secretion of ACTH by the pituitary or corticotropin-releasing hormone (CRH) by the hypothalamus (see Fig. 128-3). It is characterized by a low plasma cortisol level with a low circulating ACTH level. Although CRH in the hypophyseal portal system cannot be measured, it is likely to be increased.

Adrenal insufficiency may be further characterized as acute or chronic (Box 128-12). The most common cause of acute adrenal insufficiency is the exogenous administration of glucocorticoids, which results in suppression of the HPA axis. The degree of suppression varies on the basis of the pharmacokinetics, dose, and duration of the steroid administered. Larger doses of agents with longer half-lives and an extended course of therapy will prolong the suppression of the HPA axis. Adrenal insufficiency has been reported to occur in patients receiving prednisone in doses of as little as 25 mg twice a day for 5 days. It should, however, be anticipated to occur in patients who receive more than 30 mg/day for 3 weeks or more. The time for HPA axis recovery after exogenous suppression is highly variable, with durations ranging from several days to a year.

Adrenal insufficiency may be due to any underlying physiologic stressor, such as surgery, medications, trauma, respiratory distress, hypothermia, myocardial infarction, sepsis, hypoglycemia, pain, depression, and exogenous steroid withdrawal (after suppressed HPA axis). Etomidate, an intravenous imidazole agent, has been associated with acute adrenal insufficiency. Etomidate is a selective inhibitor of adrenal 11β-hydroxylase, the enzyme that converts deoxycorticosteroid to cortisol. For this reason, continuous infusions are not recommended. Bolus administration for rapid sequence intubation is regarded as safe, despite rare case reports of associated acute adrenal insufficiency.

Clinical Features

Clinical manifestations of primary and secondary adrenal insufficiency share some nonspecific features: fatigue, weakness, anorexia, nausea, vomiting, intestinal cramps, and dizziness are common complaints at presentation (Box 128-13). Both also result in hyponatremia from different mechanisms: aldosterone deficiency and sodium wasting in primary adrenal insufficiency, and low cortisol level and free water retention in secondary adrenal insufficiency.

Primary adrenal insufficiency, however, characteristically has more pronounced clinical manifestations than secondary adrenal insufficiency. More specific to primary adrenal insufficiency are skin hyperpigmentation (particularly in areas exposed to the sun or subject to friction or pressure), salt craving, hyperkalemia, and acidosis. In primary adrenal insufficiency, patients have symptoms related to deficiency of glucocorticoids, mineralocorticoids, and androgens. Patients with mineralocorticoid insufficiency may show signs of sodium and volume depletion (e.g., orthostatic hypotension and tachycardia). In secondary adrenal insufficiency,
mineralocorticoid production is usually preserved, and patients more often present with pale skin, loss of axillary and pubic hair, decreased libido, and impotence.

With secondary adrenal insufficiency, glucocorticoid deficiency and low ACTH concentrations may result in hypotension and hyponatremia with normal potassium levels. Patients with secondary adrenal insufficiency have normal levels of aldosterone, sex hormones, and catecholamines.

Diagnostic Strategies

Several tests are available to assist in confirming suspected cases of adrenal insufficiency. Whether in screening for chronic disease or in the workup for an acutely ill patient, cortisol measurement is the mainstay for an accurate diagnosis. Measurement of cortisol in the ACTH stimulation test is the standard and most convenient method. The test is based on the inability of the adrenal gland to
secrete appropriate amounts of cortisol after administration of corticotropin. The test cannot differentiate between primary and secondary adrenal insufficiency because the HPA axis is bypassed and therefore will not alter endogenous ACTH. Baseline cortisol concentrations are obtained before and 30 and 60 minutes after intravenous or intramuscular administration of ACTH 250 μg. Testing leads to ACTH concentrations of more than 1000 times the normal physiologic peak for adrenal cortex responsiveness.

Random basal serum cortisol concentrations are of limited value for assessment of HPA axis reserve but can confirm an intact adrenocortical reserve if basal morning concentrations are above 500 nmol/L. Cortisol levels peak between 6 AM and 8 AM, which is the appropriate time to draw blood for determination of a cortisol level. With cortisol concentration measurements between 100 and 500 nmol/L, further dynamic testing is indicated. More than 90% of cortisol is protein bound, so changes in protein binding can affect total measured serum cortisol concentrations without affecting free cortisol concentrations.

Mild to moderate hyponatremia with levels typically above 120 mEq/L is seen in primary adrenal insufficiency. Aldosterone deficiency leads to sodium wasting, and decreased cortisol levels lead to increased antidiuretic hormone, resulting in increased water absorption. Hyperkalemia may be seen in primary adrenal insufficiency secondary to low circulating aldosterone concentrations, but it is not seen in secondary causes when aldosterone is not affected.

Differential Considerations

Because of the vague and nonspecific symptoms, the differential diagnosis of hypoadrenalism is extensive. Many of the presenting signs and symptoms resemble other difficult to diagnose conditions as well. The wasting associated with chronic adrenal insufficiency resembles that of anorexia nervosa or an occult carcinoma. The generalized weakness, fatigue, and myalgias can be confused with chronic fatigue syndrome, polymyalgia rheumatica, myopathy, hypothyroidism, or influenza syndromes.

Lack of recognition of acute adrenal crisis with refractory hypotension can result in evaluations for sepsis, gastrointestinal bleeding, myocardial ischemia, or anaphylaxis. Abdominal pain in crisis may be clinically indistinguishable from an acute abdomen, especially if it is precipitated by adrenal hemorrhage. The headache and visual field cuts in pituitary apoplexy may resemble a hemorrhagic stroke. Finally, the constellation of symptoms seen in acute adrenal insufficiency (weakness, malaise, fatigue, nausea, dizziness, and arthralgias) is also present in steroid withdrawal syndrome. Because both can occur with the cessation of chronic glucocorticoid, a proper history is critical to distinguish between the two disease processes.

Management

Patients with adrenal insufficiency require hormone replacement to correct a lack of circulating glucocorticoid and mineralocorticoid without exceeding therapeutic levels. In primary adrenal insufficiency, first-line treatment is hydrocortisone (Box 128-14). In adults, the typical oral dose is 30 mg daily. To mimic natural diurnal adrenal variation, two thirds of the daily dose is usually given in the morning and one third in the late afternoon.
Minercorticoid should also be replaced in the form of fludrocortisone at 50 to 200 µg/day. In the setting of fever, infection, or intercurrent illness, the dose of hydrocortisone is doubled. In severe illness, it is commonly increased to 75 to 150 mg daily.

Whereas definitive treatment of secondary adrenal insufficiency is directed at replacement of missing hormone (ACTH or CRH) at the level of the hypothalamus or pituitary, simple steroid hormone replacement is administered in the ED setting. Steroid tapering is necessary when gradual downregulation of the HPA axis has been provoked by exogenous glucocorticoids. There is no universally recommended method for tapering of steroids.

In acute disease, emergency management of hypoadrenalism includes recognition and treatment of life-threatening cardiac rhythm disturbances, intravascular volume replacement, correction of electrolyte disturbances, correction of glucose concentration, and administration of glucocorticoids. Dexamethasone 4 mg or hydrocortisone 100 mg is administered as an intravenous bolus.

Disposition

The nonspecific symptoms of hypoadrenalism make diagnosis difficult in the ED. Most patients with mild symptoms who are not acutely ill may be discharged for outpatient evaluation and treatment.

In the severely ill patient, identification of the disease process and any underlying cause is critical. Because the lack of aggressive therapy carries a high mortality rate, admission to an ICU setting is required.

KEY CONCEPTS

Hyperthyroidism

- Thyroid hormone exerts effects on nearly every organ system. A high degree of suspicion is needed to diagnose hyperthyroidism.
- The laboratory evaluation of choice is determination of TSH concentration with free T4 and T3 levels. Total T4 and T3 levels are of limited utility.
- Thyroid storm is a life-threatening thyrotoxic crisis that requires prompt recognition and aggressive therapy as well as identification and treatment of any precipitating cause, such as infection.
- The order of medication administration in thyroid storm is critical. Iodine can precipitate thyroid storm and must be given a minimum of 1 hour after thionamide therapy (PTU or methimazole) has been administered. As such, the typical order is beta-blocker (propranolol), PTU or methimazole, then iodine (SSKI, Lugol’s solution).

Hypothyroidism

- Hypothyroidism results from either lack of stimulation of the thyroid gland (central or secondary hypothyroidism) or intrinsic gland dysfunction limiting hormone production (primary hypothyroidism).
- Signs and symptoms of hypothyroidism range from asymptomatic to overt organ failure, which can lead to death.
- Determination of an elevated TSH level is the most sensitive and single best screening test to confirm the diagnosis of primary hypothyroidism.
- Replacement with levothyroxine (T4) remains the treatment of choice and resolves most physical and psychological signs and symptoms in most patients.
- Myxedema coma is a life-threatening event that is most often precipitated by some stressful event in patients with untreated or undertreated hypothyroidism. Aggressive treatment with thyroid hormone replacement must be initiated often solely on clinical findings.

Adrenal Insufficiency

- Clinical manifestations of both primary and secondary adrenal insufficiency may be vague and nonspecific and require a high index of suspicion for diagnosis.
- Predominant complaints include fatigue, weakness, dizziness, nausea, vomiting, and other nonspecific gastrointestinal symptoms.
- Patients with primary adrenal insufficiency characteristically have more pronounced clinical manifestations and skin hyperpigmentation. Measurement of cortisol in the ACTH stimulation test is the standard and most convenient method to assist in confirming the diagnosis.
- Refractory hypotension in the acutely ill patient may be the only clue to adrenal insufficiency and is readily treated with the intravenous administration of glucocorticoids (dexamethasone 4 mg or hydrocortisone 100 mg IV).

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


