Hyperthyroidism and Thyrotoxicosis

Danielle Devereaux, MD*, Semhar Z. Tewelde, MD

Hyperthyroidism is defined as the excess production and release of thyroid hormone by the thyroid gland resulting in inappropriately high serum levels. The disproportionate amount of thyroid hormone leads to an accelerated metabolic state. The most common causes include diffuse toxic goiter (Graves disease), toxic multinodular goiter (Plummer disease), and toxic adenoma. Thyrotoxicosis also refers to a hypermetabolic state that results in excessive amounts of circulating thyroid hormone, but includes extrathyroidal sources of thyroid hormone such as exogenous intake or release of preformed stored hormone. Thyroiditis, inflammation of the thyroid gland resulting in release of stored hormone, is a frequent cause of thyrotoxicosis. The clinical presentation of thyrotoxicosis varies from asymptomatic (subclinical) to life-threatening (thyroid storm). Thyroid storm is a true endocrine emergency. The diagnosis is based on history, clinical signs and symptoms, and laboratory analyses including thyroid-stimulating hormone (TSH), free T4 (thyroxine), and T3 (triiodothyroxine).

Hyperthyroidism is a medical condition characterized by an overproduction and release of thyroid hormones, leading to a state of increased metabolic activity. The most common causes include Graves disease, Plummer disease, and toxic adenoma. Thyrotoxicosis, a term that encompasses an excess of thyroid hormone, can also arise from extrathyroidal sources like exogenous intake or release of preformed hormone. Thyroiditis, an inflammation of the thyroid gland that leads to hormone release, is a common cause of thyrotoxicosis.

Thyroid hormone affects virtually every organ system and can result in a wide array of complaints that can be challenging to identify. However, when undiagnosed, serious complications can occur, including delirium, insomnia, anorexia, osteoporosis, muscle weakness, atrial fibrillation, congestive heart failure (CHF), thromboembolism, altered mental status, cardiovascular collapse, and death. Populations at increased risk for severe sequelae include pregnant women, children, and the elderly.

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KEYWORDS

• Hyperthyroidism • Thyrotoxicosis • Thyroid storm • Thyroiditis • Graves disease

KEY POINTS

• Thyroid storm is uniformly fatal if untreated and, even with treatment, mortality ranges from 20% to 50%.
• Consider thyroid storm in any ill patient with signs and symptoms of a hypermetabolic state.
• Be wary in the elderly, children, and pregnant patients who may present with subtle or atypical symptoms of thyroid storm.
essential that the emergency medicine provider has a high clinical suspicion for hyperthyroidism and thyrotoxicosis in patients with a myriad of seemingly unrelated symptoms, especially when coupled with dysautonomia. Thyroid storm needs to be identified rapidly and treated aggressively to avoid multiorgan dysfunction and death.\textsuperscript{5}

**EPIDEMIOLOGY**

The prevalence of thyrotoxicosis in the United States is estimated at 1.2%, which comprises 0.5% symptomatic and 0.7% subclinical.\textsuperscript{6} Occurrences are seen at all ages but presentation peaks between 20 and 50 years of age secondary to the higher prevalence of Graves disease. Toxic multinodular goiter typically occurs after age 50 years, as opposed to toxic adenoma, which presents at a younger age. All forms of thyroid disease are more common in women. Graves disease is the most common cause of thyrotoxicosis in the United States, accounting for 60% to 80% of cases, whereas subacute thyroiditis accounts for 15% to 20%, toxic multinodular goiter accounts for 10% to 15%, and toxic adenoma accounts for 3% to 5%.\textsuperscript{7} Of those with thyrotoxicosis only 1% to 2% develop thyroid storm.\textsuperscript{8} Although the overall incidence of thyroid storm is low, the morbidity and mortality associated with the diagnosis make it a disease state that all emergency medicine physicians should be adept at identifying and treating.

**PATHOPHYSIOLOGY**

The production and release of thyroid hormones is regulated by a sensitive negative feedback loop involving the hypothalamus, pituitary gland, and thyroid gland (Fig. 1). The hypothalamus releases thyroid-releasing hormone (TRH), which stimulates the pituitary to release TSH, in turn stimulating the thyroid gland to release thyroid hormones, T4 and T3. The increased production of thyroid hormone normally causes inhibition of TRH and TSH release by the hypothalamus and pituitary respectively. Disruption of this delicate system leads to additional production and release of thyroid hormone and subsequent hyperthyroidism.

The production of thyroid hormones in the thyroid gland depends on iodine.\textsuperscript{3} Dietary iodide is transported into cells and converted to iodine. The iodine is then bound to thyroglobulin by thyroid peroxidase and subsequently forms monoiiodotyrosine (MIT)
and diiodotyrosine (DIT). The MIT and DIT are coupled to form T4 and T3 respectively. T3 is more biologically active and is typically formed in the periphery by conversion of T4 to T3. In the serum, thyroid hormone is typically bound to protein and inactive. Any process that increases the amount of unbound (free) thyroid hormone has the potential to cause thyrotoxicosis.

**CAUSES**

Graves disease is the most common cause of hyperthyroidism in developed countries. It is an autoimmune condition in which antibodies against the TSH receptor cause unopposed stimulation of the thyroid gland. The result is excess production of T4 and T3, an enlarged thyroid gland, and increased iodide uptake. The usual negative feedback loop is not effective because the antibody is directed against the TSH receptor. Individuals with a family history of hyperthyroidism or other autoimmune diseases such as pernicious anemia, myasthenia gravis, type I diabetes mellitus, and celiac disease have an increased propensity of developing Graves.

Toxic multinodular goiter (TMNG) is an important cause of hyperthyroidism. It is caused by unwarranted release of thyroid hormones from multiple autonomously functioning nodules in the thyroid gland. It is more common in areas of dietary iodine deficiency (third-world countries) and in the elderly (poor diet). This condition has an indolent progression and symptoms are typically mild with only slight increase of thyroid hormones above normal. TMNG is more common than Graves disease in the elderly.

Subacute thyroiditis is inflammation of the thyroid gland that typically follows a viral upper respiratory infection and causes additional release of preformed thyroid hormone. Patients typically present with fatigue, sore throat, and upper respiratory symptoms, followed by fever, neck pain, and neck swelling. It is the inflammation of the thyroid gland that causes thyroid hormone to leak into the circulation and subsequent thyrotoxicosis. The disease is usually self-limited but may lead to persistent hypothyroidism.

Toxic nodular goiter (toxic adenoma) is the result of a single nodule in the thyroid gland that is a hyperfunctioning adenoma and produces a surplus of thyroid hormone. Similar to TMNG, this is more common in areas of iodine deficiency. The increased thyroid hormone levels usually decrease TSH, but not to undetectable levels. The normal thyroid gland tissue has no iodine uptake visualized on an iodine uptake study because normal thyroid hormone production is suppressed via the negative feedback loop. However, the adenoma, which functions independently, appears as a single hot nodule with increased iodine uptake.

There are several additional causes of thyrotoxicosis that are rare but deserve consideration. Iodine-induced hyperthyroidism is the result of one or more areas of autonomously functioning thyroid tissue that occur after administration of iodine, classically iodinated contrast material. The excess iodine provides increased substrate for production of thyroid hormones. It is more common in areas with endemic goiter and iodine deficiency. It is possible for iodine to act as an immune stimulator leading to autoimmune thyroid disease and subsequent hyperthyroidism. High iodine intake is associated with increased prevalence of Graves disease. Patients typically present with a painless goiter.

Postpartum thyroiditis is inflammation of the thyroid gland following delivery. It is a transient form of hyperthyroidism that can develop 6 weeks to 6 months postpartum with a significant chance of recurrence in subsequent pregnancies. Patients present with painless goiter and typically have significant family history of autoimmune disease.
Suppurative thyroiditis is an infection of the thyroid gland typically caused by bacteria but can be caused by fungus, mycobacteria, or parasites. It is most common in immunocompromised individuals or those with underlying thyroid disease. It presents with a tender erythematous anterior neck mass, fever, dysphagia, and dysphonia.

Some other rare causes of thyrotoxicosis should be considered in the differential when clinically appropriate. Beta human chorionic gonadotropin (B-hCG) can stimulate the TSH receptor. High levels of B-hCG can be found with molar hydatidiform pregnancies and choriocarcinoma, which can lead to thyrotoxicosis. Follicular thyroid carcinoma, TSH-secreting pituitary tumors, and struma ovarii can all lead to thyrotoxicosis. Thyrotoxicosis factitia is thyrotoxicosis caused by exogenous ingestion of thyroid hormone, either intentionally or accidentally. There have been anecdotal reports of patients inappropriately using thyroid hormone to lose weight.

**CLINICAL PRESENTATION**

Thyroid hormone increases tissue thermogenesis and basal metabolic rate. Thyrotoxicosis creates a hypermetabolic state in which T3 and free T4 have widespread multiorgan effects. The spectrum of physical manifestations depends on a variety of factors including patient age and duration of illness, and can range from asymptomatic in subclinical disease to life threatening in thyroid storm. The degree of increase of circulating thyroid hormone has not been shown to correlate reliably with symptom severity. Younger patients tend to present with overt symptoms of sympathetic stimulation such as anxiety, restlessness, and tremor, whereas older patients tend to present with less obvious clinical manifestations. Elderly patients may lack adrenergic symptoms and present with depression, fatigue, and weight loss termed apathetic hyperthyroidism. Patients typically have an assortment of complaints varying from specific ailments related to one organ system to nonspecific constitutional symptoms (Table 1). There is a wide range of symptoms and differential diagnoses to consider based on clinical presentation.

Hyperthyroidism can have serious effects on the nervous system. Altered mental status and cognitive impairment can present subtly. In one review of elderly patients with hyperthyroidism, dementia and confusion were found in 33% and 18% of patients, respectively. Studies in younger individuals showed that patients with newly diagnosed hyperthyroidism had lower cognitive scores compared with age-matched controls. Seizures, nervousness, anxiety, tremors, and emotional lability are other neurologic consequences. However, patients are frequently misdiagnosed with psychiatric or substance abuse disorders before correct identification of hyperthyroidism. The emergency medicine physician should consider screening patients with new-onset psychiatric symptoms for hyperthyroidism. More than 50% of patients complain of muscle weakness and easy fatigability. The shoulders and pelvic girdle are most severely affected. Patients complain that it is difficult to climb stairs, rise out of the seated position, or comb their hair. These reports can sometimes be mistakenly attributed to neuromuscular disorders. There have even been case reports of hypokalemic periodic paralysis related to thyrotoxicosis that improved with treatment of hyperthyroidism.

Thyroid hormone has significant effects on cardiovascular hemodynamics. Being a lipophilic hormone it easily diffuses across the cytoplasmic membrane of target cells including cardiomyocytes. Hyperthyroidism increases expression of myocardial sarcoplasmic reticulum calcium-dependent adenosine triphosphatase (ATP) increasing myocardial chronotropy (heart rate) and inotropy (contractility), resulting in high left ventricular ejection fraction and cardiac output. It remains unclear whether thyroid hormone causes sensitivity to catecholamines, but it alone can alter
cardiac metabolism and function independently of beta-adrenergic stimulation.\textsuperscript{17} The hypermetabolic state that develops leads to consumption of oxygen, production of metabolic end products such as lactic acid, and arterial smooth muscle relaxation.\textsuperscript{15} Systemic vascular resistance consequently decreases, activating the renin-angiotensin system to counteract the decrease and reabsorb sodium, thus expanding the blood volume.\textsuperscript{15} The net effect is an increased preload and decreased afterload.\textsuperscript{18} Untreated, sustained volume overload and increased cardiac work leads to a compensatory increase in left ventricular mass or hypertrophy.\textsuperscript{18} Right heart failure can ensue from the increase in pulmonary artery and right-side filling pressures.\textsuperscript{18,19}

Cardiovascular symptoms most commonly include palpitations with an increased resting heart rate and exaggeration during exercise.\textsuperscript{19} Sinus tachycardia is most commonly encountered, but atrial fibrillation is the more common dysrhythmia seen
with advanced patient age, male sex, valvular disease, and coronary artery disease.\textsuperscript{20} Dysrhythmias such as flutter, supraventricular tachycardia, and ventricular tachycardia are uncommon.\textsuperscript{15} Long-standing thyroid disease symptoms can include exercise intolerance, dyspnea on exertion, and anginalike chest pain. The cause of this is 2-fold. The surplus of energy needed for exertional activities is limited because of poor cardiac reserve resulting from the resting hypermetabolic demands of the body. Sustained tachycardia inevitably causes decreased cardiac contractility, abnormal diastolic compliance, and pulmonary congestion.\textsuperscript{21} Prolonged hemodynamic disarray caused by excessive levels of thyroid hormone can progress to left ventricular dysfunction; however, clinically significant CHF remains a rare event.\textsuperscript{20} In severe hyperthyroidism or thyroid storm, CHF occurs predominately in patients with a preexisting heart disease such as ischemic, hypertensive, or alcohol cardiomyopathy, and the increased metabolic demands further impair the already weakened myocardium.\textsuperscript{21} Most cases of CHF are reversible and improve with treatment of both the primary hyperthyroid state and the heart failure. First line in controlling the cardiac chronotropic effects of excess thyroid hormone are $\beta$-blockers (eg, propranolol). Diuretics (eg, furosemide) are recommended as an adjunctive agent in patients who present with volume overload. In rare circumstances, patients may present with both atrial fibrillation and poor left ventricular function; digoxin may then prove an integral therapy.\textsuperscript{21}

Hyperthyroidism can seldom unmask silent conditions. New-onset atrial fibrillation, angina, or heart failure should never be considered solely secondary to thyroid dysfunction until structural disease has been excluded. However, in most patients, symptoms are the result of thyroid disease and not underlying heart disease. Symptoms typically resolve with appropriate thyroid therapy. Cardiovascular ailments have recently been shown to cause an effect on circulating thyroid hormone levels in patients without any thyroid abnormalities.\textsuperscript{22} Decreased serum T3 concentrations in patients with heart failure have been found to be proportional to the severity of the New York Heart Association (NYHA) functional classification.\textsuperscript{23} Recent studies show that a low T3 level is a powerful predictor of mortality in patients with NYHA class III to IV heart failure.\textsuperscript{22,24}

Amiodarone, an antiarrhythmic agent rich in iodine content and structurally similar to levothyroxine, is a well-known culprit of thyroid derangements. Amiodarone-induced hyperthyroidism (AIH) is much more common and challenging to treat than amiodarone-induced hypothyroidism.\textsuperscript{25,26} AIH is noteworthy for its 3-fold increased risk for major adverse cardiovascular events.\textsuperscript{27} Two forms of AIH exist: type I occurs in patients with preexisting thyroid disease or those living in iodine-deficient areas, and type II is a form of thyroiditis mediated by proinflammatory cytokines.\textsuperscript{17} Treatment of AIH with both iodine and antithyroid drugs has marginal effectiveness.\textsuperscript{27} Steroid therapy has some proven benefit.\textsuperscript{28} Discontinuation of amiodarone and/or total thyroidectomy is often the most effective means of reversal.\textsuperscript{29}

The cardiac disorders caused by thyrotoxicosis can subsequently affect the lungs. High-output heart failure can secondarily cause dilatation of the pulmonary artery and precipitate pulmonary arterial hypertension (PAH).\textsuperscript{21} Slight increases in pulmonary artery pressure at rest are common in patients with thyrotoxicosis, and the pressure usually increases significantly during exercise. The potential for severe PAH attributable to thyrotoxicosis alone remains unclear. Excess thyroid hormone also alters pulmonary function by weakening respiratory muscles, increasing airway resistance, and decreasing lung compliance.

Thyrotoxicosis can have significant effects on the gastrointestinal tract. Excess sympathetic stimulation can lead to increased motor contractions in the intestine causing increased intestinal transit time and diarrhea. Nausea and vomiting are
frequent complaints. Dysphagia can occur as a result of decreased closure of upper esophageal sphincter and decreased propulsion of pharyngeal muscles. Large goiters can physically compress adjacent structures such as the esophagus, leading to dysphagia, and the trachea, leading to respiratory compromise.

Thyrotoxicosis can lead to significant issues with the reproductive system, most notably infertility. Women with excess thyroid hormone can present with anovulation, oligomenorrhea, menometrorrhagia, and amenorrhea. Men have symptoms related to estrogen excess, including gynecomastia, decreased libido, and spider angiomas. Postmenopausal women can have severe osteoporosis, which can predispose to fractures.

**CLINICAL EXAMINATION**

A detailed and thorough physical examination is important in the evaluation of thyrotoxicosis because it may reveal a specific cause. There are a variety of physical examination findings that, when combined, can lead to diagnosis of thyrotoxicosis (see Table 1). Particular attention should be given to the examination of neck and eyes, as well as the neurologic, cardiac, pulmonary, and integumentary systems. The thyroid is a butterfly-shaped gland located in the anterior neck with the isthmus inferior to the cricoid cartilage and the gland wrapping around the trachea. On physical examination it is important to assess size, nodularity, tenderness, and symmetry. The gland is normally soft and nontender. In Graves disease the thyroid is symmetrically enlarged, firm, and a bruit may be auscultated. TMNG reveals an enlarged but soft thyroid. Individual nodules may sometimes be palpated but usually nodules are revealed on ultrasonography. If the examination reveals an enlarged tender gland, then clinicians should consider subacute thyroiditis or suppurative thyroiditis depending on clinical presentation.

Ophthalmologic examination may reveal multiple abnormalities. The classic presentation of Graves disease includes exophthalmos, which is severe proptosis from enlargement of the extraocular muscles. Less significant proptosis can occur with other causes of thyrotoxicosis from sympathetic hyperactivity elevating the levator palpebrae superioris muscle. All patients may appear to stare and have a lid lag, but patients with Graves disease present with unique eye findings. Graves ophthalmopathy or orbitopathy can include proptosis, chemosis, conjunctival injection, periorbital or lid edema, and vasodilation of the conjunctiva. Inability to close the eyelids may lead to corneal ulceration. Diplopia can occur from proptosis and extraocular muscle dysfunction. The presence of increased thyroid hormones and ophthalmopathy strongly suggests the diagnosis of Graves disease.

The neurologic assessment may reveal an agitated, restless, nervous, or anxious patient. In thyroid storm, the alteration of mental status can range from catatonia and depression to frank psychosis. Physical examination may reveal a fine resting tremor that with exertion or an outstretched arm becomes more noticeable and significant. The tremor may also be noted in the feet, tongue, and facial muscles. Muscle group and strength testing may identify decreased bulk and proximal limb weakness, respectively. Hyperreflexia is common. Chronic disease can cause atrophy most notable in the thenar and hypothenar muscles.

Nearly every patient with thyrotoxicosis has a resting tachycardia. Increased blood flow through the aortic outflow tract often leads to a systolic murmur. A systolic scratchy sound, the Means-Lerman scratch, is less common and is thought to result from the hyperdynamic pericardium against the pleura, mimicking pericarditis. In the case of thyroid storm, patients may develop murmurs from significant mitral
regurgitation and/or tricuspid regurgitation. Increase in systolic and decrease in diastolic blood pressures result in a widened pulse pressure that can extenuate the intensity of the normal heart sounds and produce a hyperactive precordium with bounding peripheral pulses. The carotid upstroke is rapid and brisk. In the elderly, an irregularly irregular pulse may be appreciated.

Patient may appear dyspneic from tachypnea secondary to the body’s increased oxygen demand and carbon dioxide production. There are case reports of worsening asthma and chronic obstructive pulmonary disease exacerbations in the setting of thyrotoxicosis. Just as patients with pulmonary disease can tire from prolonged respiratory exacerbations, profound thyrotoxicosis can lead to respiratory muscle weakness, diaphragmatic fatigue, and pulmonary decompensation.

Thyrotoxicosis causes deposition of glycosaminoglycans in the dermis of the lower extremities, which causes nonpitting edema, erythema, and thickening of the skin. The skin can resemble an orange peel and is referred to as pretibial myxedema. There is no associated tenderness or pruritus. Pretibial myxedema is a rare finding associated with hyperthyroidism from Graves disease.

**UNIQUE POPULATIONS**

The diagnosis of hyperthyroidism is difficult in elderly patients because the usual signs and symptoms of a hypermetabolic state may be absent. Elderly patients typically present with involvement of a single system or have subtle nonspecific symptoms that may be attributed to the natural aging process. Most have small or nonpalpable goiter on physical examination. Apathetic hyperthyroidism, which is uncommon but most frequently seen in the elderly, is characterized by apathetic facies, small goiter, depression, muscle weakness, weight loss, and absence of ophthalmopathy. The diagnosis of thyrotoxicosis in elderly patients is difficult and a high level of suspicion is necessary. Unexplained change in mental status, mood, or behavior; unexplained weight loss; myopathy; new-onset atrial fibrillation or heart failure; and overall incongruous symptoms should always prompt further work-up for thyroid dysfunction.

A euthyroid pregnant patient typically experiences resting tachycardia, systolic flow murmur, widened pulse pressure, heat intolerance, increased perspiration, tachypnea, dyspnea, and mood changes, all secondary to the normal physiologic changes associated with pregnancy. Therefore, thyrotoxicosis is exceedingly difficult to diagnose during pregnancy. Hyperthyroidism in pregnancy can be a significant cause of fetal morbidity and mortality. If untreated during pregnancy, it can cause neonatal hypothyroidism from TSH antibodies that cross the placenta, destroying the fetal thyroid gland. It can also result in premature labor, low birth weight, and eclampsia. It is important to consider hyperthyroidism in pregnant patient with goiter, tachycardia greater than 100 beats per minute that does not improve with Valsalva maneuver, weight loss, or onycholysis. Graves disease complicates 1 in 500 pregnancies.

Thyrotoxicosis in the neonate occurs in 1% of pediatric hyperthyroidism cases. It is most commonly secondary to maternal Graves disease and is the result of transplacental passage of maternal antibodies. Neonates are typically premature, of low birth weight, and have early skeletal maturation. Affected neonates usually have prominent eyes and small, uniformly enlarged thyroid glands. They may have microcephaly, enlarged ventricles, triangular facies, and frontal bossing. Additional physical findings may include tachycardia, bounding pulses, cardiomegaly, CHF, jaundice, hepatosplenomegaly, and thrombocytopenia. Clinical manifestations of thyrotoxicosis in children and adolescents include ophthalmopathy (most commonly), failure to thrive, tachycardia, increased gastrointestinal motility, muscle weakness, hyperreflexia, sleep
disturbance, and distractibility. In addition, children may have acceleration of linear growth and epiphyseal maturation. The most common cause of thyrotoxicosis in children is Graves disease.

**THYROID STORM**

Thyroid storm is a life-threatening form of thyrotoxicosis that usually occurs following a precipitating event. The most common trigger is infection or sepsis. Patients customarily have a prior history of thyrotoxicosis but thyroid storm can be the initial clinical presentation. Untreated thyroid storm is uniformly fatal. Thyroid storm with treatment has improved outcomes but mortality remains significant at 20% to 50%. The clinical features of thyroid storm are exaggerated signs and symptoms of thyrotoxicosis. Altered mental status is the hallmark. Mental status changes including agitation, emotional lability, delirium, convulsions, and chorealike abnormal movements. Patients can also have autonomic dysfunction depicted by excessive diaphoresis, severe hyperthermia, hypertension, and intractable dysrhythmias. This condition can lead to hypotension and cardiovascular collapse. Other metabolic and electrolyte derangements seen are hyperglycemia from catecholamine-mediated inhibition of insulin, leukocytosis in absence of infection, and hypercalcemia secondary to bone resorption. Specific criteria for identifying thyroid storm were elucidated by Burch and Wartofsky and include hyperpyrexia, tachycardia, atrial fibrillation, CHF, gastrointestinal dysfunction, central nervous system disturbance, and precipitant history (Fig. 2). Thyrotoxicosis with concomitant alteration in sensorium or cardiopulmonary decompensation is thyroid storm until proved otherwise.

**DIAGNOSTIC ASSESSMENT**

Confirming the diagnosis of hyperthyroidism in the emergency department can be achieved by obtaining TSH and free T4 (Table 2). Approximately 95% of patients with thyrotoxicosis have an increased T4. A small subset (5%) of patients have normal

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**Fig. 2.** Point scale for the diagnosis of thyroid storm. (From Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am 1993;22(2):263–77; with permission.)
T4 and increased T3 only known as T3 toxicosis. Therefore, if the clinical suspicion is high for hyperthyroidism but the T4 is normal, obtain a total T3 because the patient likely has T3 toxicosis. Most cases of hyperthyroidism have suppressed TSH because of the negative feedback loop. However, pituitary-dependent hyperthyroidism has normal TSH with increased T4. Subclinical hyperthyroidism has decreased TSH with normal free T4. It is common for systemic disease to suppress the TSH, so it is important to repeat thyroid studies before starting therapy for subclinical disease. There is no clinical usefulness to obtaining a total T4 in the emergency department. Many drugs interact with thyroid hormone–binding proteins and can confound the diagnosis.

There are additional studies that can be obtained to help confirm the diagnosis in complicated cases. Serum thyroglobulin levels can be obtained to differentiate thyrotoxicosis from factitious thyroid disease. Autoantibodies can be obtained to determine the type of autoimmune disease that is present. Imaging studies can be performed to elucidate the specific cause of hyperthyroidism, but these tests are generally not practical or warranted in the emergency department. Patients who do not fit the clinical picture of Graves disease should have a radioactive iodine uptake study or thyroid

### Table 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>TSH</th>
<th>FT4</th>
<th>FT3</th>
<th>Other Investigation/Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves disease</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>RAIU: increased uptake Thyroid peroxidase antibodies: increased TSH-receptor antibodies: positive</td>
</tr>
<tr>
<td>Toxic thyroid adenoma hot nodule</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>RAIU: functioning nodule with suppression of other tissue</td>
</tr>
<tr>
<td>TMNG</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>RAIU: enlarged gland with multiple active nodules</td>
</tr>
<tr>
<td>Subacute or granulomatous thyroiditis</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>RAIU: low uptake Tg level: markedly raised</td>
</tr>
<tr>
<td>Factitious thyroxine-induced thyrotoxicosis</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>RAIU: low uptake Tg levels: absent</td>
</tr>
<tr>
<td>Iodine-induced hyperthyroidism</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Hx of amiodarone use or exposure to radiocontrast agents RAIU: low uptake</td>
</tr>
<tr>
<td>Hyperthyroidism, untreated</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>RAIU: high uptake</td>
</tr>
<tr>
<td>Hyperthyroidism, T3 toxicosis</td>
<td>Low</td>
<td>Normal</td>
<td>High</td>
<td>RAIU: normal or high uptake</td>
</tr>
<tr>
<td>Euthyroid, on exogenous thyroid hormone</td>
<td>Normal</td>
<td>Normal on T4, Low on T3</td>
<td>High on T3, Normal on T4</td>
<td>RAIU: low uptake</td>
</tr>
</tbody>
</table>

**Abbreviations:** Hx, history; RAIU, radioactive iodine uptake; Tg, thyroglobulin.

T4 and increased T3 only known as T3 toxicosis. Therefore, if the clinical suspicion is high for hyperthyroidism but the T4 is normal, obtain a total T3 because the patient likely has T3 toxicosis. Most cases of hyperthyroidism have suppressed TSH because of the negative feedback loop. However, pituitary-dependent hyperthyroidism has normal TSH with increased T4. Subclinical hyperthyroidism has decreased TSH with normal free T4. It is common for systemic disease to suppress the TSH, so it is important to repeat thyroid studies before starting therapy for subclinical disease. There is no clinical usefulness to obtaining a total T4 in the emergency department. Many drugs interact with thyroid hormone–binding proteins and can confound the diagnosis.
scan. Ultrasonography with Doppler flow can be used when radiation exposure is contraindicated, as in pregnancy and breastfeeding. In addition, the use of iodinated contrast studies should be avoided in thyrotoxicosis given that additional iodine substrate can increase serum thyroid levels.34

In resource-scarce settings in which imaging may not be available, the ratio of T3 to T4 is useful in assessing cause. When the gland is hyperactive, more T3 than T4 is produced. Therefore, in Graves disease and toxic nodular goiter, the ratio (ng/mg) of T3 to T4 should be greater than 20. Subacute and painless thyroiditis causes release of preformed hormone but does not generate new thyroid hormone, so the ratio of T3 to T4 is less than 20.

MANAGEMENT

Therapy for thyrotoxicosis depends on the underlying cause. Treatment strategies include antithyroid drugs, radioactive iodine, thyroid surgery, and medications for symptom control (Table 3).1 The most commonly used antithyroid drugs are the thiouramides, propylthiouracil (PTU) and methimazole (MMI).35 Thionamides block the synthesis of T4 by inhibiting organification of tyrosine residues. In addition, PTU blocks peripheral conversion of T4 to T3. MMI dosage is 10 to 30 mg per day in once-daily dosing. PTU dosage is 200 to 400 mg per day divided 2 to 3 times per day. Thyroid function tests are repeated every 4 weeks during initial medication management so dosages can be adjusted accordingly. More than one-third of patients go into remission for 10 years or longer after starting antithyroid medication. Common adverse effects of thionamides include abnormal taste, pruritus, urticaria, fever, and arthralgia. Less commonly, patients develop cholestatic jaundice, thrombocytopenia, lupuslike syndrome, hepatitis, and agranulocytosis.

Radioactive iodine therapy can be used in Graves disease, toxic nodules, and TMNGs. It is the most common form of therapy for adults with Graves disease. Therapy is provided by a single oral dose of radioactive iodine that is absorbed by the thyroid gland and causes organ-specific inflammation. Thyroid fibrosis and tissue destruction occur gradually over several months. The major drawback to radioactive iodine is hypothyroidism, which is an expected complication requiring lifelong L-thyroxine replacement therapy. Hypothyroidism occurs within 4 to 12 months of therapy. Radioactive iodine therapy does not require hospitalization and is noninvasive. The thyroid is the only tissue capable of absorbing the iodine so side effects are minimal. Iodine therapy is contraindicated in pregnancy, breastfeeding, and in patients with severe ophthalmopathy.

Thyroid surgery is rapid and effective but invasive and expensive. Patients need to be euthyroid before surgery. It can cause permanent hypothyroidism and transient hypocalcemia requiring calcium supplementation. Surgical complications include recurrent laryngeal nerve damage and permanent hypoparathyroidism. Because of the efficacy of antithyroid medication and radioactive iodine therapy, surgery is performed less frequently. It is generally reserved for pregnant women intolerant of thionamides, children with severe disease, severe ophthalmopathy, amiodarone-induced refractory disease, or unstable cardiac conditions.1 In the past, stress in the operating room during surgery was the most common cause of thyroid storm, with a mortality of 50%. Thyroid storm during surgery is exceedingly rare now with preoperative therapies including propranolol, antithyroid medication, and iodine.

Symptom control can be achieved with a variety of medications. The American Thyroid Association with the American Association of Clinical Endocrinologists published guidelines for the management of hyperthyroid symptoms.1 A primary
### Table 3
Treatment strategies

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Drug</th>
<th>Action</th>
<th>Neonates</th>
<th>Children</th>
<th>Adults</th>
<th>Thyroid Storm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antithyroid agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Neovite</td>
<td>Prevents production of more T₄ and T₃ in the thyroid, and blocks the conversion of T₄ to T₃ outside the thyroid</td>
<td>5–10 mg/kg/d divided Q8 h PO</td>
<td>Initial: 5–7 mg/kg/d divided Q8 h PO</td>
<td>Initial: 100–200 mg PO Q6–8 h</td>
<td>500–1000 mg loading dose, then 250 mg PO/NG/OG or PR Q4–6 h</td>
</tr>
<tr>
<td>Methimazole</td>
<td></td>
<td>Prevents production of more thyroid hormone</td>
<td>NA</td>
<td>Initial: 0.4–0.7 mg/kg/d PO divided Q8 h</td>
<td>Initial: 10–20 mg PO Q8–12 h</td>
<td>60–80 mg/d PO/NG/OG</td>
</tr>
<tr>
<td><strong>Iodides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lugol solution</td>
<td></td>
<td>Blocks release of stored thyroid hormone from thyroid gland</td>
<td>1 drop PO Q8 h</td>
<td>—</td>
<td>4–8 drops Q6-8 h PO/NG/OG</td>
<td>10 drops Q12 h PO/NG/OG</td>
</tr>
<tr>
<td>Saturated solution of potassium iodide</td>
<td></td>
<td></td>
<td>—</td>
<td>1–5 drops Q8 h PO/NG/OG</td>
<td>5–10 drops Q6-8 h PO/NG/OG</td>
<td>5–10 drops Q6-8 h PO/NG/OG</td>
</tr>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td>Blocks conversion of T₄ to T₃</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
<td>2 mg/kg PO/IV Q6 h</td>
<td>—</td>
<td>2 mg Q6 h PO</td>
<td>2 mg Q6 h IV or PO/NG/OG</td>
</tr>
<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
<td></td>
<td>2 mg/kg/d PO divided Q6–12 h</td>
<td>0.5–1 mg/kg/d divided Q6–12 h</td>
<td>10–40 mg PO Q6–8 h</td>
<td>1 mg/min IV as required, then 60–80 Q4 h PO/NG/OG</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td>Reduces symptoms caused by a heightened response to catecholamines; blocks conversion of T₄ to T₃</td>
<td>2 mg/kg/d PO divided Q6–12 h</td>
<td>0.5–1 mg/kg PO daily (maximum dose 100 mg/d)</td>
<td>25–100 mg PO daily (maximum dose 200 mg/d)</td>
<td>NA</td>
</tr>
<tr>
<td>Atenolol</td>
<td></td>
<td></td>
<td>—</td>
<td>0.5–1 mg/kg PO daily (maximum dose 100 mg/d)</td>
<td>25–100 mg PO daily (maximum dose 200 mg/d)</td>
<td>NA</td>
</tr>
<tr>
<td>Esmolol</td>
<td></td>
<td></td>
<td>100–500 μg/kg/min infusion</td>
<td>100–500 μg/kg/min IV load then 25–100 μg/kg/min infusion</td>
<td>500 μg/kg/min for 1 min, then 50–100 μg/kg/min</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** IV, intravenous; NG, nasogastric tube; OG, orogastric tube; PO, by mouth; PR, per rectum; Q, every.
recommendation was to consider β-blockers in all symptomatic patients, especially the elderly and patients with resting heart rates of more than 90 beats per minute. The use of propranolol, atenolol, and metoprolol has been shown to decrease heart rate, systolic blood pressure, muscle weakness, and tremor, and to improve irritability and emotional lability. The calcium channel blockers verapamil and diltiazem have been shown to decrease heart rate in patients for whom β-blockers were contraindicated, but can cause profound hypotension and should be used cautiously.

Treatment of subacute thyroiditis is initially aspirin or other nonsteroidal antiinflammatory medication. Some patients require glucocorticoid therapy given as a once-daily burst for 1 week and then tapered over 4 weeks. β-Blocking medication such as propranolol can be used for symptom control. The thyrotoxicosis typically resolves spontaneously and no further treatment is needed. Subacute thyroiditis should not be treated with antithyroid medication from the emergency department.

Antithyroid medications and β-blockers are the primary treatment of thyrotoxicosis during pregnancy.¹ Radioactive iodine therapy is contraindicated. Surgery is reserved for women who are unable to tolerate antithyroid medication. PTU and MMI can both be used during pregnancy and have similar rates of neonatal hypothyroidism. However, MMI has been associated with scalp defects when used in the first trimester. Therefore, a woman with hyperthyroidism who desires pregnancy should be started on PTU and can be switched to MMI if desired after 12 weeks’ gestation.¹ PTU is the drug of choice for breastfeeding mothers given that it is secreted in breast milk to a lesser extent because it is more protein bound. β-Blocking agents can be used for symptom control during pregnancy but risks and benefits must be weighed carefully. β-Blockers cross the placenta and can cause in utero growth restriction, prolonged labor, bradycardia, hypotension, hypoglycemia, and prolonged hyperbilirubinemia in the infant.

Children and adolescents with hyperthyroidism can be treated with antithyroid medication, radioactive iodine, or surgery as clinically indicated. Almost all children requiring antithyroid medication should be treated with MMI. Before initiating therapy, children should have baseline complete blood count and liver function tests. Although MMI has better safety profile than PTU, it is associated with adverse risks including allergic reactions, rashes, myalgias, arthralgias, and rarely agranulocytosis. PTU is associated with hepatotoxicity and subsequent liver failure. Its use is contraindicated in children. There have been case reports of fatal fulminant hepatic necrosis.¹ Symptomatic control can be achieved with β-blockers in children (see Table 3). Neonatal thyrotoxicosis is almost uniformly a result of maternal Graves disease and the subsequent transplacental passage of maternal thyroid-stimulating antibodies. As a result, hyperthyroidism is usually self-limited because antibodies decline by 3 to 4 months of age. Treatment typically involves symptomatic care (see Table 3).

Thyroid storm is a life-threatening hypermetabolic state with significant morbidity and mortality.⁶,³² Prompt recognition and initiation of therapy is crucial for good outcomes. Medication management is directed at controlling the overactive thyroid gland and blocking peripheral effects of thyroid hormones (see Table 3). These patients are typically critical and should have rapid placement of large-bore intravenous access, supplemental oxygen, and cardiac monitoring. Aggressive volume resuscitation should be started immediately with the exception of patients with concomitant heart failure, in which case use of fluids should be judicious. Because cardiovascular collapse is often the cause of decompensation, β-blockers should be initiated first. β-Blockers control patient symptoms and sympathetic hyperactivity. The initial β-blocker should be propranolol with esmolol infusion as an alternate choice. High-dose steroid should be given early to help augment vascular tone. Both β-blockers
and steroids reduce peripheral conversion of T4 to T3. PTU is the preferred medication for thyroid storm because it also decreases peripheral conversion of T4 to T3. It additionally decreases the synthesis of T4 and T3 within the thyroid gland. PTU and MMI are available in oral preparations only. They can be given orally, by nasogastric/orogastric tube, or per rectum as clinically indicated. The initial loading dose for PTU is 600 to 1000 mg, then 250 mg every 4 hours. MMI can be given as 20 mg every 4 hours. Thionamides are effective at inhibiting synthesis of new thyroid hormone but are ineffective at decreasing preformed stored hormones. Iodine and lithium are effective at blocking release of preformed hormones from the thyroid gland. Iodine should be given 1 hour after PTU or MMI to reduce the risk of increasing thyroid hormone production by providing more substrate. Acetaminophen and cooling devices can be used for hyperthermia. Salicylates should be avoided because they can increase free thyroid hormone levels by decreasing thyroid-binding protein in the serum. If an underlying infectious cause is suspected early broad-spectrum antibiotics must not be forgotten and should be started as early as possible. Patients with refractory life-threatening symptoms can undergo hemodialysis if medical management is ineffective.

**DISPOSITION**

Patients with thyroid storm require admission to the intensive care unit. Patients with symptomatic thyrotoxicosis may require inpatient admission if initial therapy in the emergency department fails to normalize vital signs, if symptoms are severe, or if the patient does not have adequate follow-up. Patients requiring antithyroid medication who are stable for discharge should be referred to the endocrinology clinic for further evaluation and medication management. Patients with subacute thyroiditis should not be started on antithyroid medication and can be followed up with endocrinology for further evaluation and management.

### Hyperthyroidism pearls

1. Thyroid storm has a broad differential. Keep the following in mind:
   a. Acute pulmonary edema
   b. Heat stroke
   c. Malignant hyperthermia
   d. Sepsis/septic shock
   e. Sympathomimetic overdose
   f. Serotonin syndrome
   g. Tachyarrhythmias
2. The classic triad of thyroid storm is high fever, exaggerated tachycardia out of proportion to fever, and central nervous system dysfunction or cerebral encephalopathy.
3. Wait at least 1 hour after antithyroid medication before giving iodide or serum thyroid hormone levels may inadvertently be increased, exacerbating the issue.
4. Plasmapheresis, charcoal hemoperfusion, and plasma exchange can be used to rapidly decrease thyroid hormone levels in refractory cases.
5. Do not use aspirin or other salicylates for fever control in thyroid storm because they can increase serum hormone levels.
SUMMARY

Hyperthyroidism and thyrotoxicosis are hypermetabolic conditions that cause significant morbidity and mortality. The diagnosis can be difficult because symptoms can mimic many other disease states leading to inaccurate or untimely diagnoses and management. Thyroid storm is the most severe form of thyrotoxicosis, hallmarked by altered sensorium, and, if untreated, is associated with significant mortality. Thyroid storm should be considered in the differential of any patient presenting with altered mental status. The emergency medicine physician who can rapidly recognize the signs and symptoms of thyrotoxicosis, identify the precipitating event, appropriately and comprehensively begin medical management, and facilitate disposition will undoubtedly save a life.

REFERENCES