## SPECIAL POPULATIONS

### PREGNANT WOMEN

Overt hypothyroidism is seen in about 1% to 2% of pregnant women.[8] Subclinical hypothyroidism is seen in another 2.5%.[9]

Most cases of hypothyroidism during pregnancy have the same cause as in hypothyroidism in general. Pregnancy increases the requirement of thyroid hormone because of the increased rate of metabolism in the mother and the transplacental transport of thyroid hormone, which is essential for the development and maturation of the different organs of the fetus. For women who are being treated for hypothyroidism, the dose of thyroxine should be increased approximately by 30% as soon as the pregnancy is confirmed.[10]

Thyroid function test results during pregnancy may be difficult to interpret. This is because pregnant patients may have a higher production of thyroid hormone from stimulation of the gland by human chorionic gonadotropin, which has a similar structure to that of thyroid-stimulating hormone. On top of that, increased estrogen during pregnancy results in higher levels of thyroid-binding globulin, which transports thyroid hormone in the blood. Therefore, a normal thyroid hormone level in a pregnant woman may not mean the patient is euthyroid, especially if the patient has symptoms of hypothyroidism. Thyroid hormone replacement may still be required in this case.

Hypothyroidism is diagnosed in pregnancy if patients have symptoms and, in general, have high levels of thyroid-stimulating hormone and low free thyroxine. Subclinical hypothyroidism in pregnancy can be identified if the test results show high levels of thyroid-stimulating hormone and normal free thyroxine. Subclinical hypothyroidism should be treated to ensure healthy pregnancy.

Synthetic thyroxine, which is identical to the thyroxine made by the thyroid gland, is used for pregnant women. It is safe for the fetus. Pregnant women with existing hypothyroidism require an increased dose of thyroxine during pregnancy, and the thyroid function is usually checked every 8 weeks.

### ELDERLY PATIENTS

Age, the presence of cardiac comorbidities, and a high dose of thyroxine are associated with a poor outcome in myxedema crisis.[10] Standard doses of thyroxine, and especially of triiodothyronine, can precipitate cardiac arrhythmias. Start with no more than half the recommended dose of thyroxine or triiodothyronine for elderly patients.

### PATIENTS WITH CARDIAC DISEASE

Thyroxine has fewer cardiac effects than triiodothyronine. Thyroxine is the preferred choice for thyroid hormone replacement in patients with heart disease.

### THE ASYMPTOMATIC PATIENT WITH A PALPABLE NODULE IDENTIFIED IN THE ED

Solitary thyroid nodules are a common physical finding in the general population. Although most are benign colloid nodules that will disappear over time, a small percentage of solitary nodules are thyroid carcinomas. Biopsy results identify 70% of nodules to be benign, 5% to be malignant, and the remainder to be cytologically indeterminate.[11] Therefore, referral for fine-needle aspiration biopsy is indicated for all patients with palpable nodules.

### LEVOTHYROXINE OVERDOSE

Synthetic levothyroxine is the most widely used agent for thyroid replacement. Deaths from overdose have not been reported. When taken in overdose, symptoms do not occur until 24 hours later as a result of metabolic conversion of thyroxine to triiodothyronine. Treatment is not standardized. For acute ingestion, activated charcoal can be given. Cholestyramine can decrease fecal elimination, and propranolol can control tachycardia and anxiety. Contact your local poison control center for specific treatment recommendations.

**Acknowledgment:** The author gratefully acknowledges the contributions of Horace K. Liang, the author of this chapter in the previous edition.

## REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 229

# Hyperthyroidism

Alzamani Mohammad Idrose

## INTRODUCTION AND EPIDEMIOLOGY

Thyroid hormone affects all organ systems and is responsible for increasing metabolic rate, heart rate, and ventricle contractility, as well as muscle and central nervous system excitability. Two major types of thyroid hormones are thyroxine and triiodothyronine. Thyroxine is the major form of thyroid hormone. The ratio of thyroxine to triiodothyronine released in the blood is 20:1. Peripherally, thyroxine is converted to the active triiodothyronine, which is three to four times more potent than thyroxine.

Hyperthyroidism refers to excess circulating hormone resulting only from thyroid gland hyperfunction, whereas thyrotoxicosis refers to excess circulating thyroid hormone originating from any cause (including thyroid hormone overdose).

Thyroid storm is the extreme manifestation of thyrotoxicosis. This is an acute, severe, life-threatening hypermetabolic state of thyrotoxicosis caused either by excessive release of thyroid hormones causing adrenergic hyperactivity or altered peripheral response to thyroid hormone following the presence of one or more precipitants.

The mortality of thyroid storm without treatment is between 80% and 100%, and with treatment, it is between 15% and 50%.

Primary hyperthyroidism is caused by the excess production of thyroid hormones from the thyroid glands. Secondary hyperthyroidism is caused by the excess production of thyroid-releasing hormones or thyroid-stimulating hormones in the hypothalamus and pituitary, respectively (**Tables 229-1** and **229-2**).

In the case of thyroid storm, the most common underlying cause of hyperthyroidism is Graves' disease (85% of all hyperthyroidism cases in the United States). It is caused by the thyrotropin receptor antibodies that stimulate excess and uncontrolled thyroidal synthesis and secretion of thyroid hormones. It occurs most frequently in young women (10 times more common in women compared with men) at any age group.[1]

## PATHOPHYSIOLOGY

The pathophysiologic mechanisms underlying the shift from uncomplicated thyrotoxicosis to thyroid storm are not entirely clear. However, they involve adrenergic hyperactivity either by increased release of thyroid hormones (with or without increased synthesis) or increased receptor sensitivity. Many of the signs and symptoms are related to adrenergic hyperactivity. Patients with thyroid storm reportedly have relatively higher levels of free thyroid hormones as opposed to those with uncomplicated thyrotoxicosis. The total thyroid hormone level may or may not be increased in these patients.

When there is excess of thyroid hormones, circulating thyroxin and triiodothyronine are taken into the cytoplasm of cells. Thyroxin is converted to its active form, triiodothyronine. Within the cytoplasm, the triiodothyronine then exerts its effect by passing into the nucleus and binding to thyroid hormone receptors or thyroid hormone–responsive elements to induce gene activation and transcription.[2] The receptors receiving the hormone will stimulate changes specific to the tissue.

**TABLE 229-1 Causes of Hyperthyroidism: Primary and Secondary Hyperthyroidism**

| | |
|---|---|
| **Primary Hyperthyroidism** | |
| Graves' disease (toxic diffuse goiter) (**Figure 229-1**) | Most common of all hyperthyroidism (85% of all cases)<br>Associated with diffuse goiter, ophthalmopathy, and local dermopathy |
| Toxic multinodular goiter | Second most common cause of hyperthyroidism |
| Toxic nodular (adenoma) goiter (**Figure 229-2**) | An enlarged thyroid gland that contains a small rounded mass or masses called nodules with overproduction of thyroid hormone |
| Thyroiditis | Inflammation of the thyroid gland |
| Hashimoto's thyroiditis | Initially gland is overactive (hyperthyroidism state), but this is usually followed by a state of hypothyroidism |
| Subacute painful thyroiditis (de Quervain's thyroiditis) | |
| Subacute painless thyroiditis | |
| Radiation thyroiditis | |
| **Secondary Hyperthyroidism** | |
| Thyrotropin-secreting pituitary adenoma | Thyroid gland stimulated to produce hormones |

In the pituitary gland, thyroid hormones exert negative regulation on the transcription of the genes for the subunit and the common subunit of thyroid-stimulating hormone, resulting in thyroid-stimulating hormone suppression.

During thyroid storm, precipitants such as infection, stress, myocardial infarction, or trauma will multiply the effect of thyroid hormones by freeing thyroid hormones from their binding sites or increasing receptor sensitivity.

### THYROID STORM PRECIPITATION

The precipitants of thyroid storm are as shown in **Table 229-3.** In some patients undergoing radioactive iodine therapy for hyperthyroidism, thyroid storm may ironically occur following treatment due to withdrawal of antithyroid drugs, release of thyroid hormones from damaged thyroid follicles, or the effect of radioactive iodine itself.

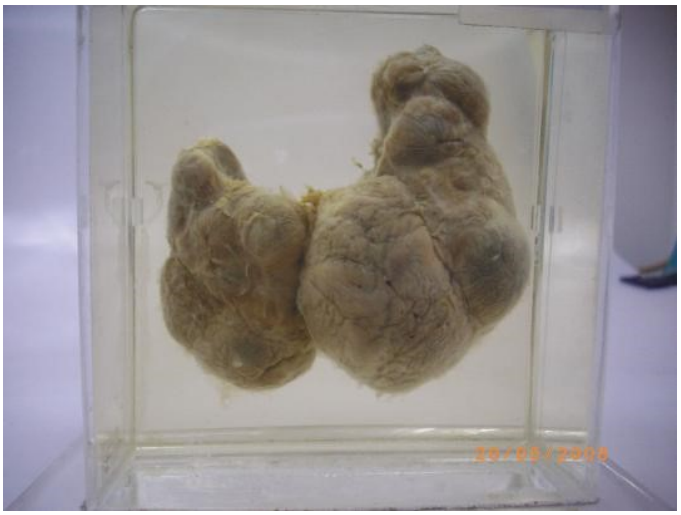


**FIGURE 229-1.** Pathology specimen of Graves' disease: most common cause of hyperthyroidism. Diffuse swelling is evident. [Image used with permission of the University of Malaya Pathology Museum.]

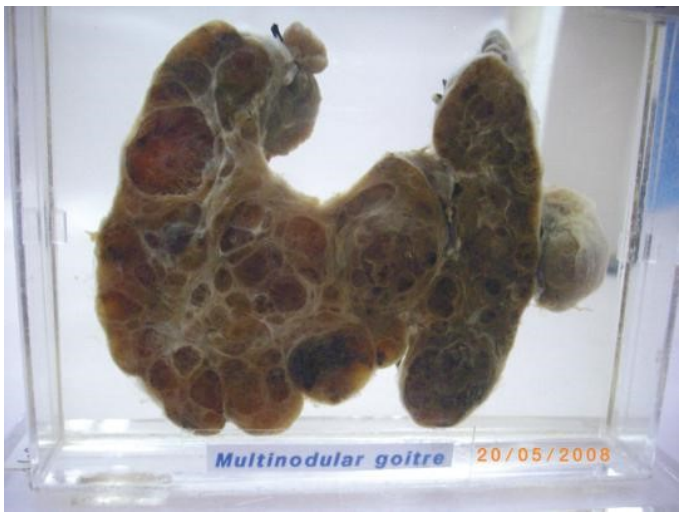



**FIGURE 229-2.** Pathology specimen of multinodular goiter: second most common cause of hyperthyroidism. Multinodular appearance can be seen. [Image used with permission of the University of Malaya Pathology Museum.]

## CLINICAL FEATURES

### HISTORY AND COMORBIDITIES

The patient may only complain of constitutional symptoms such as generalized weakness and fatigue. Heat intolerance, diaphoresis, fever, voracious appetite but poor weight gain, anxiety, emotional lability, palpitations, diarrhea, and hair loss are common historical features. If there is a history of hyperthyroidism, ask about treatment and compliance with medication.

### PHYSICAL EXAMINATION

In general, patients often appear toxic and agitated. The signs and symptoms of hyperthyroidism patients are as shown in **Table 229-4**.

**TABLE 229-2 Other Causes of Hyperthyroidism**

| | |
|---|---|
| **Nonthyroidal Disease** | |
| Ectopic thyroid tissue (struma ovarii)/teratoma | A rare form of mature teratoma that contains mostly thyroid tissue |
| Metastatic thyroid cancer | Stimulates production of thyroid hormones |
| Human chorionic gonadotropin | Secreting hydatidiform mole |
| **Drug Induced** | |
| Iodine | Iodine-induced thyrotoxicosis (called *Jod-Basedow disease*)<br>After treatment of endemic goiter patients with iodine or stimulation of thyroid hormones from use of iodine-containing agents such as radiographic contrast agents |
| Amiodarone | Contains iodine; may cause either thyrotoxicosis or hypothyroidism |
| α-Interferon<br>Interleukin-2 | During treatment for other diseases, such as viral hepatitis and human immunodeficiency virus infection |
| Thyrotoxicosis factitia | Munchausen-like; thyroid hormone is taken by patient to fake illness |
| Ingestion of meat containing beef thyroid tissue | Cow thyroid tissue contains thyroid hormones |
| Excessive thyroid hormone ingestion | |

**TABLE 229-3 Precipitants of Thyroid Storm**

| | |
|---|---|
| **Systemic insult** | **Cardiovascular insult** |
| Infection | Myocardial infarction |
| Trauma | Cerebrovascular accidents |
| General surgery | Pulmonary embolism |
| **Endocrinal insult** | **Obstetrics related** |
| Diabetic ketoacidosis | Parturition |
| Hyperosmolar coma | Eclampsia |
| **Drug or hormone related** | **Radioactive iodine therapy** |
| Withdrawal of anti-thyroid medication | |
| Iodine administration | |
| Thyroid gland palpation | |
| Ingestion of thyroid hormone | |
| **Unknown cause in up to 25% of cases** | |

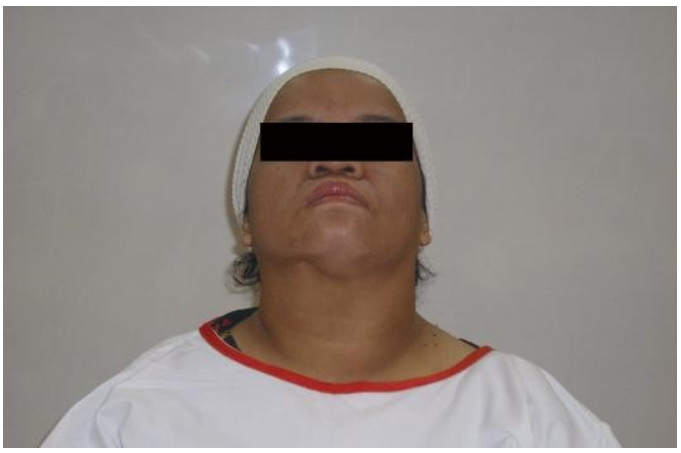


**FIGURE 229-3.** Goiter with hyperthyroidism symptoms: patient has large solitary toxic adenoma on the left lobe.

**TABLE 229-4 Symptoms and Signs of Thyrotoxicosis**

| Affected System | Symptoms | Signs |
|---|---|---|
| Constitutional | Lethargy<br>Weakness<br>Heat intolerance | Diaphoresis<br>Fever<br>Weight loss |
| Neuropsychiatric | Emotional lability<br>Anxiety<br>Confusion<br>Coma<br>Psychosis | Fine tremor<br>Muscle wasting<br>Hyperreflexia<br>Periodic paralysis |
| Ophthalmologic | Diplopia<br>Eye irritation | Lid lag<br>Dry eyes<br>Exophthalmos<br>Ophthalmoplegia<br>Conjunctival infection |
| Endocrine: thyroid gland (**Figure 229-3**) | Neck fullness<br>Tenderness | Thyroid enlargement<br>Bruit |
| Cardiorespiratory | Dyspnea<br>Palpitations<br>Chest pain | Widened pulse pressure<br>Systolic hypertension<br>Sinus tachycardia<br>Atrial fibrillation or flutter<br>High output heart failure |
| Gastrointestinal | Diarrhea<br>Yellowish sclera | Hyperactive bowel sound<br>Jaundice |
| Reproductive | Oligomenorrhea<br>Decreased libido | Gynecomastia<br>Telangiectasia |
| Gynecologic | Menorrhagia<br>Irregularity | Sparse pubic hair |
| Hematologic | Pale skin | Anemia<br>Leukocytosis |
| Dermatologic | Hair loss | Pretibial myxedema*<br>Warm, moist skin<br>Palmar erythema<br>Onycholysis |

*Pretibial myxedema may be present in 5% of patients with Graves' disease.

As for thyroid storm, the additional signs and symptoms apart from those evident in thyrotoxicosis are as shown in **Table 229-5**.

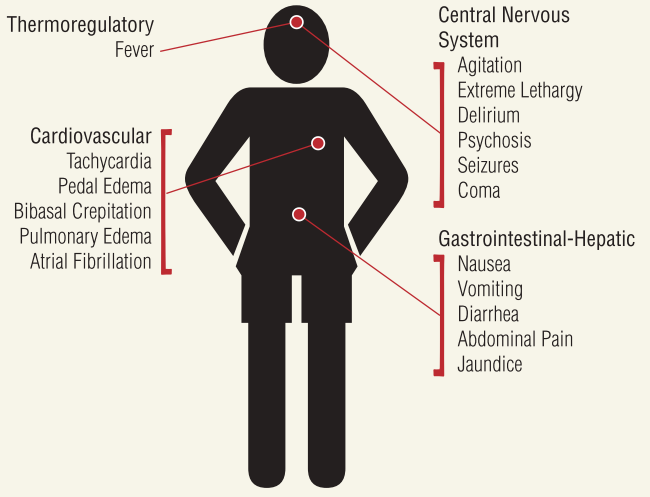
Fever is often present in thyroid storm and may be quite high. It may herald the onset of thyrotoxic crisis in previously uncomplicated disease. Palpitations, tachycardia, and dyspnea are common. A pleuropericardial rub may be heard. The direct inotropic and chronotropic effects of thyroid hormone on the heart cause increased blood volume, increased contractility, and increased cardiac output. Enhanced contractility produces elevations in systolic blood pressure and pulse pressure, leading to a dicrotic or water-hammer pulse. Atrial fibrillation occurs in 10% to 35% of thyrotoxicosis cases.[3,4]

The severity of exophthalmos does not necessarily parallel the magnitude of thyroid dysfunction but reflects the responsible autoimmune process. Not all hyperthyroidism patients present with goiter. A goiter is not present with exogenous administration of thyroid hormone and apathetic thyrotoxicosis. Likewise, the presence of a goiter does not necessarily confirm the diagnosis of thyrotoxicosis. Thyroid gland tenderness can be found in inflammatory conditions such as subacute thyroiditis.[5]

## DIAGNOSING THYROID STORM

Thyroid storm is a clinical diagnosis for patients with preexisting hyperthyroidism. In determining whether or not a patient has thyroid storm, the main systems to concentrate on are the **thermoregulatory system**

**TABLE 229-5 Presenting Signs and Symptoms of Thyroid Storm**



(rise in temperature), **CV system** (ranging from tachycardia to atrial fibrillation and congestive cardiac failure), **CNS** (ranging from being agitated to seizure), and the **GI-hepatic system** (ranging from nausea to vomiting and jaundice) (**Table 229-5**). **Table 229-6** provides a scoring system for thyroid storm as compared with severe thyrotoxicosis. A score ≥45 is highly suggestive of thyroid storm. The system is sensitive in picking up thyroid storm but is not very specific.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of thyroid storm is shown in **Table 229-7**.

**TABLE 229-7 Differential Diagnosis for Thyroid Storm**

| |
|---|
| Infection and sepsis |
| Sympathomimetic ingestion (e.g., cocaine, amphetamine, ketamine drug use) |
| Heat exhaustion |
| Heat stroke |
| Delirium tremens |
| Malignant hyperthermia |
| Malignant neuroleptic syndrome |
| Hypothalamic stroke |
| Pheochromocytoma |
| Medication withdrawal (e.g., cocaine, opioids) |
| Psychosis |
| Organophosphate poisoning |

## LABORATORY TESTING

**Serum Thyroid-Stimulating Hormone Level** In **primary hyperthyroidism**, the thyroid-stimulating hormone level is low as a result of the negative feedback mechanism toward a high thyroid hormone level. Nevertheless, a low thyroid-stimulating hormone level by itself is not diagnostic, as serum thyroid-stimulating hormone may be reduced as a result of chronic liver or renal disease or the effect of certain drugs such as glucocorticoids, which reduce thyroid-stimulating hormone secretion.

In **secondary hyperthyroidism**, thyroid-stimulating hormone is increased because of increased production in the pituitary.

**Free Thyroid Hormone Levels: Free Thyroxine and Free Triiodothyronine** A low thyroid-stimulating hormone with an elevated free thyroxine confirms primary hyperthyroidism. A high thyroid-stimulating hormone with high free thyroxine denotes secondary causes of hyperthyroidism. On the other hand, a low thyroid-stimulating hormone with a normal free thyroxine but elevated free triiodothyronine is also diagnostic of triiodothyronine thyrotoxicosis. Triiodothyronine thyrotoxicosis occurs in <5% of patients who have thyrotoxicosis in North America.[5] Total thyroid hormone levels are not necessarily acutely elevated when the transition from uncomplicated thyrotoxicosis to thyroid storm occurs.

**Triiodothyronine Resin Uptake** Triiodothyronine resin uptake estimates free thyroxine levels by measuring unoccupied thyroxine-binding globulin sites and is also used to account for changes in binding protein concentration. A higher triiodothyronine resin uptake value means less thyroxine-binding globulin is available, implying the presence of hyperthyroidism.

**Total Thyroid Hormone Level of Thyroxine and Triiodothyronine** Total serum thyroxine and triiodothyronine (bound and unbound) are increased in thyrotoxicosis. Eighty percent of circulating triiodothyronine is derived from mono-deiodination of thyroxine in peripheral tissues, whereas 20% emanates from direct thyroidal secretion. Both thyroxine and triiodothyronine are then bound to proteins in the form of thyroxine-binding globulin, transthyretin, and albumin. Only a small fraction of the hormones are free and unbound. Laboratory measurement of total triiodothyronine and total thyroxine measures mainly protein-bound hormone concentrations. In thyroid storm, total thyroid hormone level may or may not be increased. Results also may be affected by conditions that affect protein binding. With the improved assays for free thyroxine and free triiodothyronine, there is now little indication to measure total triiodothyronine and total thyroxine.

**Thyroid Antibody Titers** Thyroid-stimulating antibodies are detected in Graves' disease. Thyroid antibody titers (to thyroid peroxidase or thyroglobulin) will help determine diagnosis.

**Ancillary Tests** Obtain a CBC, electrolytes, glucose, and renal and liver function tests to identify comorbidities, but start treatment upon suspicion of the diagnosis. In thyroid storm, CBC typically shows leukocytosis with shift to the left. Hyperglycemia tends to occur because of a catecholamine-induced inhibition of insulin release and increased glycogenolysis and rapid intestinal absorption of glucose. Mild hypercalcemia and elevated alkaline phosphatase can occur because of hemoconcentration and enhanced thyroid hormone–stimulated bone resorption.[6]

Thyrotoxicosis also induces liver enzyme metabolism, causing raised liver enzymes. A high serum cortisol value is an expected finding in thyrotoxic individuals. This should be the normal reaction of an adrenal

**TABLE 229-6 Burch and Wartofsky's Diagnostic Parameters and Scoring Points for Thyroid Storm**

| Diagnostic Parameters | Scoring Points |
|---|---|
| **1. Thermoregulatory dysfunction** | |
| Temperature °C (°F) | |
| 37.2–37.7 (99–99.9) | 5 |
| 37.7–38.3 (100–100.9) | 10 |
| 38.3–38.8 (101–101.9) | 15 |
| 38.9–39.4 (102–102.9) | 20 |
| 39.4–39.9 (103–103.9) | 25 |
| ≥40 (≥104.0) | 30 |
| **2. CNS effects** | |
| Absent | 0 |
| Mild (agitation) | 10 |
| Moderate (delirium, psychosis, extreme lethargy) | 20 |
| Severe (seizures, coma) | 30 |
| **3. GI-hepatic dysfunction** | |
| Absent | 0 |
| Moderate (diarrhea, nausea/vomiting, abdominal pain) | 10 |
| Severe (unexplained jaundice) | 20 |
| **4. CV dysfunction** | |
| Tachycardia (beats/min) | |
| 90–109 | 5 |
| 110–119 | 10 |
| 120–129 | 15 |
| ≥140 | 25 |
| **5. Congestive heart failure** | |
| Absent | 0 |
| Mild (pedal edema) | 5 |
| Moderate (bibasilar rales) | 10 |
| Severe (pulmonary edema) | 15 |
| **6. Atrial fibrillation** | |
| Absent | 0 |
| Present | 10 |

Scoring system:
Score of ≥45: Highly suggestive of thyroid storm.
Score of 25–44: Suggestive of impending storm.
Score of <25: Unlikely to represent thyroid storm.
(Reproduced with permission from Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am* 22: 263, 1993.)

gland to a body under stress. The finding of an abnormally low cortisol level in a patient with Graves' disease should raise suspicion of coincidental adrenal insufficiency.

**Imaging** Chest radiograph can be done to rule out infection as a precipitant for thyroid storm. A thyroid sonogram with Doppler flow can be done to assess thyroid gland size, vascularity, and the presence of nodules. Typically, a thyroid gland secreting excessive hormones would be enlarged. On the other hand, in the setting of subacute, postpartum thyroiditis, silent thyroiditis, or exogenous causes of hyperthyroidism, the thyroid gland is not expected to be enlarged. Nuclear medicine imaging with iodine-131 would reveal a greatly increased uptake of radioiodine as early as 1 or 2 hours after administration of the agent. CT of the brain may be necessary to exclude neurologic conditions if diagnosis is uncertain, as CNS abnormalities causing altered mental status may precipitate thyroid storm.

**Electrocardiogram in Thyrotoxicosis** Electrocardiogram findings in thyrotoxicosis most commonly include sinus tachycardia and atrial fibrillation. Sinus tachycardia occurs in approximately 40% of cases.[4] Atrial fibrillation occurs in 10% to 35% of thyrotoxicosis patients—more commonly in patients >60 years old with underlying structural heart disease.[4] Premature ventricular contractions and heart blocks may be present. Atrial premature contractions and atrial flutter may also occur.

## TREATMENT

The order of therapy in treating thyroid storm is very important with regard to the use of thionamide and iodine therapy. **Inhibition of thyroid gland synthesis of new thyroid hormone with a thionamide should be initiated before iodine therapy to prevent the stimulation of new thyroid hormone synthesis that can occur if iodine is given too soon.**

**Treatment aims are as follows:**

1. Supportive care
2. Inhibition of new hormone synthesis
3. Inhibition of thyroid hormone release
4. Peripheral β-adrenergic receptor blockade
5. Preventing peripheral conversion of thyroxine to triiodothyronine

The treatment recommendations are shown in **Table 229-8**, with specific comments in the following sections.

### TREATMENT AIM 1: SUPPORTIVE CARE

Fluid losses could result from the combination of fever, diaphoresis, vomiting, and diarrhea. Check blood glucose and if blood sugar is relatively low, IV fluids with dextrose (isotonic saline with 5% or 10% dextrose) may be given to replenish glycogen stores.

**Cholestyramine** Cholestyramine is used to inhibit thyroid hormone reabsorption. Thyroid hormone is metabolized mainly in the liver, where it is conjugated to glucuronides and sulfates. These conjugation products are then excreted in the bile. Free hormones are released in the intestine and finally reabsorbed, completing the enterohepatic circulation of thyroid hormone. In states of thyrotoxicosis, there is increased enterohepatic circulation of thyroid hormone. Cholestyramine is an anion exchange resin that decreases reabsorption of thyroid hormone from the enterohepatic circulation. Cholestyramine in combination with methimazole or propylthiouracil, causes a more rapid decline in thyroid hormone levels than standard therapy with thionamides alone.[1]

### TREATMENT AIM 2: INHIBITION OF NEW THYROID HORMONE SYNTHESIS

**Thionamides** Thionamides used for the treatment of thyrotoxicosis are either methimazole or propylthiouracil. Thionamide therapy decreases the synthesis of new hormone production but also has immunosuppressive effects.[7] Thionamides inhibit synthesis of thyroid hormones by preventing organification and trapping of iodide to iodine and by inhibiting coupling of iodotyrosines.

Methimazole has a longer half-life than propylthiouracil, permitting less frequent dosing. It presents in free form in the serum, whereas 80% to 90% of propylthiouracil is bound to albumin.[7]

The dose for methimazole is 40 to 100 milligrams given PO as loading dose followed by 20 milligrams every 4 hours. The total daily dose that should be given is 120 milligrams/d. If given PR, 40 milligrams should be crushed in aqueous solution. Although there are no commercially available parenteral formulations of the thionamides, there are case reports of methimazole being administered IV in circumstances in which the PO and PR routes of administration could not be used.[8] Methimazole was shown to have similar pharmacokinetics for both PO and IV use in normal subjects and in subjects with hyperthyroidism. In some centers, only carbimazole (which is the prodrug of methimazole) is available. If methimazole is not available, carbimazole can be used with the same potency.[9] The initial dose is 40 to 60 milligrams, followed by a maintenance dose of between 5 and 20 milligrams daily.

As for propylthiouracil, the dose for thyroid storm is 600 to 1000 milligrams given PO as a loading dose followed by 200 to 250 milligrams every 4 hours. The total daily dose that should be given is between 1200 and 1500 milligrams/d. The drug can be given by nasogastric tube or PR. Outside the thyroid gland, only propylthiouracil, not methimazole, can inhibit conversion of thyroxine to triiodothyronine.

**Warning on Use of Propylthiouracil** The U.S. Food and Drug Administration (FDA) in 2009 notified healthcare professionals of the risk of serious liver injury, including liver failure and death, with the use of propylthiouracil in adults and children. There is an increased risk of hepatotoxicity with propylthiouracil when compared with methimazole.10 Since 2010, the FDA has added a boxed warning to the prescribing information of propylthiouracil to include information about reports of severe liver injury and acute liver failure, some of which have been fatal. The FDA recommends that propylthiouracil be reserved for patients who cannot tolerate methimazole.

Propylthiouracil is preferred only in the case of pregnant patients during the first trimester, as methimazole use during this period had been associated with teratogenicity.[11] Nevertheless, methimazole is again suggested for use during the second and third trimesters of pregnancy. If propylthiouracil is used, signs and symptoms of liver injury should be closely monitored, especially in the first 6 months of therapy initiation. Its use must be discontinued immediately in cases of suspected liver injury. Propylthiouracil should not be used in children unless the patient is allergic to or intolerant of methimazole and no other treatment options are available.

### TREATMENT AIM 3: INHIBITION OF HORMONE RELEASE

**Iodine** Lugol solution, potassium iodide, ipodate (Oragrafin□), or lithium carbonate can be given to stop thyroid hormone release. **Thionamide therapy must be instituted first and these drugs only given at least 1 hour later.** Iodine therapy blocks the release of prestored hormone and decreases iodide transport and oxidation in follicular cells. Lugol solution can be given 30 to 40 drops/d divided three to four times a day. One may start with 8 to 10 drops initially. Lugol solution provides 8 milligrams of iodide per drop.

Iodinated radiographic contrast dyes that contain ipodate (Oragrafin□) 0.5 to 3 grams/d orally or IV iopanoic acid (Telepaque□) 1 gram every 8 hours for the first 24 hours followed by 500 milligrams twice a day have also been used to inhibit hormone release, and they also have the added property to effectively prevent conversion of thyroxine to triiodothyronine.

**Nevertheless, iodine-containing solution should not be given to patients with iodine overload or iodine-induced hyperthyroidism or those with amiodarone-induced thyrotoxicosis.** Lithium or potassium perchlorate may be used instead.

### TREATMENT AIM 4: PREVENTING PERIPHERAL CONVERSION OF THYROXINE TO TRIIODOTHYRONINE

The peripheral conversion of thyroxine to triiodothyronine, which is responsible for 85% of triiodothyronine present in the circulation, is blocked by propylthiouracil, propranolol, and glucocorticoid. Nevertheless, for propylthiouracil and propranolol, this effect is not quantitatively significant. Therefore, glucocorticoids such as hydrocortisone or dexamethasone are essential in treatment. Glucocorticoid use in thyroid storm also improves survival rates.[2,12] In patients who have severe thyrotoxicosis, especially in conjunction with hypotension, treatment with glucocorticoids is a standard practice because of the possibility of relative adrenal insufficiency.

**TABLE 229□8 Treatment for Thyroid Storm**

1. **Supportive care**

   General: oxygen, cardiac monitoring

   Fever: external cooling; acetaminophen 325–650 milligrams PO/PR every 4–6 h (aspirin is contraindicated because it may increase free thyroid hormone)

   Dehydration: IV fluids, IV isotonic saline with 5% dextrose may be used to replace glycogen depletion if blood sugar is low

   Nutrition: glucose, multivitamins, thiamine, including folate can be considered (deficient secondary to hypermetabolism)

   Cardiac decompensation (atrial fibrillation, congestive heart failure): rate control and inotropic agent, diuretics, sympatholytics as required

2. **Inhibition of new thyroid hormone synthesis with thionamides**

   Methimazole 40 milligrams given PO as loading dose and followed by 25 milligrams every 4 h. Total daily dose should be given: 120 milligrams/d. If given PR, 40 milligrams should be crushed in aqueous solution.

   *(Avoid methimazole for pregnant women in first trimester as it can cause teratogenic effect. It can only be used in second and third trimester of pregnancy.)*

   *or*

   PTU, a loading dose of 600–1000 milligrams given PO and followed by 200–250 milligrams every 4 h. Total daily dose should be given: 1200–1500 milligrams/d. Drug can be given via nasogastric tube or PR. (PTU also blocks peripheral conversion of thyroxin to triiodothyronine.)

   *(PTU is used for pregnant women in first trimester. PTU also has a boxed warning issued by the U.S. Food and Drug Administration in 2010 regarding its rare but severe side effect toward liver function. Methimazole is preferred as first-line treatment unless contraindicated.)*

3. **Inhibition of thyroid hormone release (at least 1 h after step 2)**

   Lugol solution 8–10 drops PO every 6–8 h

   *or*

   Potassium iodide (SSKI) five drops PO every 6 h

   *or*

   IV iopanoic acid (Telepaque□), 1 gram every 8 h for first 24 h, then 500 milligrams twice a day

   *or*

   Ipodate (Oragrafin□), 0.5–3 grams/d PO (especially useful with thyroiditis or thyroid hormone overdose)

   *or*

   Lithium carbonate (if allergic to iodine or agranulocytosis occurs with thionamides), 300 milligrams PO every 6 h (1200 milligrams/d) and subsequently to maintain serum lithium at 1 mEq/L

4. **β-Adrenergic receptor blockade**

   Propranolol IV in slow 1- to 2-milligram boluses, which may be repeated every 10 to 15 min until the desired effect is achieved. For less toxic patient, PO dose of 20 to 120 milligrams per dose or 160 to 320 milligrams/d in divided doses (contraindicated in bronchospastic disease and congestive heart failure)

   *or*

   Esmolol 500 micrograms/kg IV bolus, then 50–200 micrograms/kg/min maintenance

   *or*

   Reserpine 2.5–5.0 milligrams IM every 4–6 h, preceded by 1-milligram test dose while monitoring blood pressure (use if β-blocker contraindicated but avoid in congestive heart failure or hypotension and cardiac shock)

   *or*

   Guanethidine 30–40 milligrams PO every 6 h (use if β-blocker contraindicated but avoid in congestive heart failure, hypotension, and cardiac shock)

5. **Preventing peripheral conversion of thyroxine to triiodothyronine**

   Hydrocortisone 100 milligrams IV initially, then 100 milligrams three times/d until stable (also for adrenal replacement due to hypermetabolism)

   *or*

   Dexamethasone 2 milligrams IV every 6 h

6. **Treat precipitating event**

   All triggers of thyroid storm should be searched and treated accordingly (infection, myocardial infarct, diabetic ketoacidosis, etc.).

7. **Definitive therapy**

   Radioactive iodine ablation therapy or surgery may be necessary.

*Note:* Replacement therapy: dialysis and plasmapheresis are last resorts for patients who do not respond to treatments 1–5.

*Abbreviation:* PTU = propylthiouracil.

## TREATMENT AIM 5: β□ADRENERGIC RECEPTOR BLOCKADE

**Propranolol** can be given IV in slow 1- to 2-milligram boluses, which may be repeated every 10 to 15 minutes until the desired effect is achieved. Orally, propranolol therapy usually begins at 20 to 120 milligrams per dose or 160 to 320 milligrams/d in divided doses.

The contraindications to peripheral blockade are the same as those for other medical conditions. Exercise caution in patients with congestive cardiac failure and thyrotoxic cardiomyopathy. Complicated patients with both a tachydysrhythmia and congestive heart failure can be managed first with rate control and an inotropic agent.

## ALTERNATIVE TREATMENTS

Several alternative therapeutic agents are considered when the first-line therapies of thionamides, iodide, β-blockers, and glucocorticoids fail or cannot be used owing to toxicity or contraindicated conditions.

**Alternative Drugs for Inhibition of New Hormone Synthesis or Release** • *Potassium Perchlorate* Potassium perchlorate blocks thyroid uptake of iodine and thus interferes with the production of new hormones The perchlorate anion, ClO4–, is a competitive inhibitor of iodide transport. The recommended dose is 0.5 gram of potassium perchlorate per day.13 It is used in amiodarone-induced thyrotoxicosis for which iodine replacement is contraindicated. However, it has side effects of aplastic anemia and nephrotic syndrome.

*Lithium* In situations in which there is a contraindication to giving iodine (e.g., hypersensitivity to iodine), an alternative such as lithium can be used. In severe thyroid storm conditions, lithium can also be used in combination with propylthiouracil or methimazole. Lithium inhibits thyroid hormone release from thyroid gland. Lithium also has effects on the thyroid gland that decrease thyroid hormone synthesis, thereby increasing intrathyroidal iodine content and inhibiting coupling of iodotyrosine residues that form thyroxine and triiodothyronine. In thyroid storm, the dosing for lithium is 300 milligrams every 8 hours. To avoid lithium toxicity, lithium level should be monitored regularly every day to maintain a concentration of approximately 0.6 to 1.0 mEq/L (0.6-1.0 mmol/L). Very frequent monitoring of serum lithium levels is mandatory, especially because the serum lithium concentrations may change as the patient is rendered more euthyroid.

**Alternative Drugs for Peripheral Blockade of β-Receptor: Reserpine and Guanethidine** Reserpine or guanethidine can be used, usually in severe asthmatic patients needing treatment for thyroid storm, as they do not block β-receptors. These agents would be indicated only in rare situations in which β-adrenergic receptor antagonists are contraindicated and when there is no hypotension or evidence of central nervous system–associated mental status changes.[2] Side effects of both medications include hypotension and diarrhea.

Reserpine is an alkaloid agent that depletes catecholamine stores in sympathetic nerve terminals and the central nervous system. It can have central nervous system depressant effects. In severe asthmatics, IM reserpine, 2.5 milligrams every 4 hours, may be considered in lieu of peripheral blockade.[13] Guanethidine inhibits the release of catecholamines. Dosing for guanethidine in thyroid storm is 30 to 40 milligrams PO every 6 hours.

**Thyroid Hormone Removal** In patients who have contraindications to propylthiouracil and methimazole, such as a prior severe reaction, direct removal of thyroid hormone has been described. Plasmapheresis, charcoal hemoperfusion, resin hemoperfusion, and plasma exchange have been found to be effective in rapidly reducing thyroid hormone levels in thyroid storm.[13,14]

### IDENTIFY PRECIPITATING FACTORS

Search for infection in febrile thyrotoxic patients. Obtain an electrocardiogram to identify myocardial infarction, ischemia, or arrhythmia.

In cases of thyroid storm precipitated by diabetic ketoacidosis, myocardial infarction, pulmonary embolism, or other acute processes, appropriate management of the specific underlying problem should proceed along with the treatment of the thyrotoxicosis.[2]

### DEFINITIVE THERAPY

Definitive therapy with radioactive iodine ablation may not be able to be done for several weeks or months after treatment with iodine for thyroid storm. Close follow-up and monitoring should continue, with plans for definitive therapy to prevent a future recurrence of life-threatening thyrotoxicosis.[2]

## GUIDE FOR PREPARATION OF THYROTOXIC PATIENTS FOR EMERGENCY SURGERY

In the event that a patient has thyrotoxicosis background and requires emergent surgery, the recommendation of drug supplementation is as shown in **Table 229-9**. The supplementation is important, as surgery in a patient with hyperthyroidism may precipitate thyroid storm.

### ADVERSE SIDE EFFECTS FROM ANTITHYROID DRUGS

Common adverse side effects of the antithyroid drugs are shown in **Table 229-10**.

**TABLE 229-9 Rapid Preparation of Thyrotoxic Patients for Emergent Surgery**

| Drug Class | Recommended Drug | Dosage | Mechanism of Action | Continue Postoperatively? |
|---|---|---|---|---|
| β-Adrenergic blockade | Propranolol | 40–80 milligrams PO 3 to 4 times a day | β-Adrenergic blockade; decreased thyroxine-to-triiodothyronine conversion (high dose) | Yes |
| | *or* | | | |
| | Esmolol | 50–100 micrograms/kg/min | β-Adrenergic blockade | Change to PO propranolol |
| Thionamide | Propylthiouracil | 200 milligrams PO every 4 h | Inhibition of new thyroid hormone synthesis; decreased thyroxine-to-triiodothyronine conversion | Stop immediately after near-total thyroidectomy; continue after nonthyroidal surgery |
| | *or* | | | |
| | Methimazole | 20 milligrams PO every 4 h | Inhibition of new thyroid hormone synthesis | Stop immediately after near-total thyroidectomy; continue after nonthyroidal surgery |
| Oral cholecystographic agent | Iopanoic acid | 500 milligrams PO twice a day | Decreased release of thyroid hormone; decreased thyroxine-to-triiodothyronine conversion | Stop immediately after surgery |
| Corticosteroid | Hydrocortisone | 100 milligrams PO or IV every 8 h | Vasomotor stability; decreased thyroxine-to-triiodothyronine conversion | Taper over first 72 h |
| | *or* | | | |
| | Dexamethasone | 2 milligrams PO or IV every 6 h | Vasomotor stability; decreased thyroxine-to-triiodothyronine conversion | Taper over first 72 h |
| | *or* | | | |
| | Betamethasone | 0.5 milligram PO every 6 h, IM or IV | Vasomotor stability; decreased thyroxine-to-triiodothyronine conversion | Taper over first 72 h |

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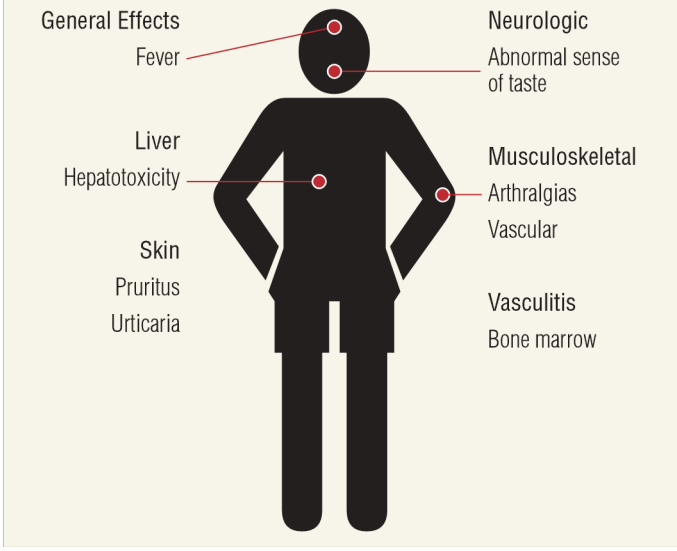
**TABLE 229-10 Common Adverse Side Effects from Antithyroid Drugs**




After surgery, the precipitating event should be determined, and definitive therapy of thyrotoxicosis should be planned.

## DISPOSITION AND FOLLOW-UP

Thyroid storm patients typically require admission to the intensive care unit. Patients with thyroid storm often have concomitant diseases precipitating the attack and require close monitoring. Complete recovery may take 1 week until circulating levels of thyroid hormones are depleted. Stable hyperthyroid patients with minimal symptoms can only be discharged for follow-up either by an endocrinologist or primary care physician, if the patient is already on medication with a clear plan of follow-up.

## SPECIAL POPULATIONS

### ELDERLY PATIENTS

Older patients may present with "apathetic" thyrotoxicosis (i.e., with some atypical symptoms, including weight loss, palpitations, weakness, dizziness, syncope, memory loss, and physical findings of sinus tachycardia or atrial fibrillation).[5] Signs and symptoms of this condition are few and subtle, and the initial appearance of disease may be single-organ failure (e.g., congestive heart failure), producing diagnostic confusion by pointing to diagnoses other than thyrotoxicosis.

### DRUG INTERACTIONS IN THYROTOXIC PATIENTS

Many drugs interfere with protein binding, including heparin, furosemide, phenytoin, carbamazepine, diazepam, salicylates, opiates, estrogens, and nonsteroidal anti-inflammatory drugs. Because of this interference with total thyroid hormone levels, free hormone concentrations are preferable in the diagnosis of thyrotoxicosis.[6]

### THYROTOXIC PATIENTS AND AMIODARONE

Amiodarone is an essential anti-arrhythmic drug used in the ED. Amiodarone is also a precipitant of thyroid storm. It is 37% organic iodine by weight, and as such, can have many effects on thyroid function. Normal maintenance doses result in iodine loads of 10 to 20 times the normal dietary requirement of iodine. Chronic use of amiodarone causes either a hypothyroid or a thyrotoxic state in 20% to 30% of patients.[15]

### THYROTOXIC PATIENTS WITH ATRIAL FIBRILLATION

The issue of anticoagulation in atrial fibrillation in the setting of thyrotoxicosis is controversial. Studies assessing the incidence of embolic events in thyrotoxic patients who have atrial fibrillation have yielded conflicting information regarding the incidence of embolism. Thyrotoxic patients who have atrial fibrillation may not be at greater risk for embolic events, compared with age-matched patients who have atrial fibrillation due to other causes.[16] Therefore, standard therapy with warfarin or aspirin would be indicated. Thyrotoxic patients may require a lower maintenance dose of warfarin than euthyroid patients because of increased clearance of vitamin K–dependent clotting factors.[17]

## REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 230

# Adrenal Insufficiency

Alzamani Mohammad Idrose

## INTRODUCTION

Te adrenal gland synthesizes steroid hormones in the cortex and catecholamines in the medulla. **Adrenal insufciency** is defciency of adrenal gland hormone production in the cortex. **Primary adrenal insufciency,** or Addison's disease, is due to intrinsic adrenal gland dysfunction and results in decreased cortisol, aldosterone, and sex hormone production. Te condition is rare, with prevalence ranging from 39 to 144 cases per million population.[1]

**Secondary adrenal insufficiency** is due to hypothalamic-pituitary dysfunction with failure to secrete corticotropin-releasing hormone and/or adrenocorticotropic hormone. This disorder results in cortisol deficiency only.

**Adrenal crisis** is a life-threatening exacerbation of adrenal insufficiency when an increased demand fails to increase hormone production.

## ADRENAL GLAND PHYSIOLOGY

The adrenal gland is made up of the cortex and medulla producing steroid hormones and catecholamines, respectively. The adrenal cortex produces three categories of steroids: the glucocorticoids (**cortisol**), mineralocorticoids (**aldosterone**), and gonadocorticoids (**sex hormones**). Glucocorticoids are produced in the zona fasciculata, and mineralocorticoids and gonadocorticoids are produced in the zona glomerulosa and zona reticularis of the adrenal cortex. The adrenal medulla produces adrenaline, noradrenaline, and a small amount of dopamine in response to stimulation by sympathetic preganglionic neurons.

**Cortisol** is secreted in response to direct stimulation by adrenocorticotropic hormone. Adrenocorticotropic hormone secretion is stimulated by corticotropin-releasing factor released from the hypothalamus. Secretion occurs in a diurnal rhythm, with higher levels secreted in the morning and lower levels in the evening. In normal circumstances, the daily cortisol equivalent is about 20 milligrams/d of hydrocortisone. Plasma cortisol suppresses the release of adrenocorticotropic hormone through negative feedback inhibition. Cortisol facilitates the stress response by affecting the heart, vascular bed, water excretion, electrolyte balance, potentiation of catecholamine action, and control of water distribution. It affects fat, protein, and carbohydrate metabolism by stimulating glycogenolysis and neoglycogenesis. It is involved in immunologic and inflammatory responses and affects calcium metabolism. It promotes growth and development but, in excess, interferes with the GI tract mucosa maintenance, leading to peptic ulcer.

**Aldosterone** secretion is controlled primarily by the renin-angiotensin system and serum potassium concentration. The renin-angiotensin system controls aldosterone levels in response to changes in