Hyperthyroidism: Diagnosis and Treatment

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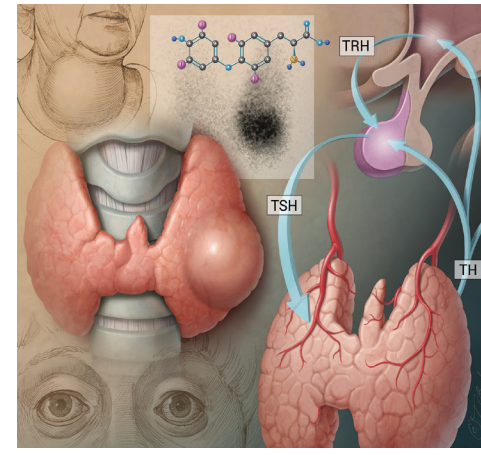
Hyperthyroidism is an excessive concentration of thyroid hormones in tissues caused by increased synthesis of thyroid hormones, excessive release of preformed thyroid hormones, or an endogenous or exogenous extrathyroidal source. The most common causes of an excessive production of thyroid hormones are Graves disease, toxic multinodular goiter, and toxic adenoma. The most common cause of an excessive passive release of thyroid hormones is painless (silent) thyroiditis, although its clinical presentation is the same as with other causes. Hyperthyroidism caused by overproduction of thyroid hormones can be treated with antithyroid medications (methimazole and propylthiouracil), radioactive iodine ablation of the thyroid gland, or surgical thyroidectomy. Radioactive iodine ablation is the most widely used treatment in the United States. The choice of treatment depends on the underlying diagnosis, the presence of contraindications to a particular treatment modality, the severity of hyperthyroidism, and the patient's preference. (*Am Fam Physician.* 2016;93(5):363-370.



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CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 351.

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▶ **Patient information:** A handout on this topic, written by the author of this article, is available at http://www.aafp.org/afp/2016/0301/p363-s1.html.

Hyperthyroidism is an excessive concentration of thyroid hormones in tissues causing a characteristic clinical state. In the United States, the overall prevalence of hyperthyroidism is 1.2%, and the prevalences of overt hyperthyroidism and subclinical hyperthyroidism are 0.5% and 0.7%, respectively.[1]

Etiology and Pathogenesis

The common endogenous causes of hyperthyroidism are Graves disease, toxic multinodular goiter, toxic adenoma, and painless thyroiditis *(Table 1)*.[1-9] Graves disease, the most common cause of hyperthyroidism in the United States,[2] is an autoimmune disorder in which thyroid-stimulating antibodies activate thyroid-stimulating hormone (TSH) receptors, triggering thyroid hormone synthesis. Risk factors for Graves disease include female sex and personal or family history of an autoimmune disorder.[2,3]

Toxic multinodular goiter is the second most common cause of hyperthyroidism in the United States and the most common cause in older persons living in iodine-deficient areas.[2] Over time, nodules arise from the frequent replication of clonogenic cells that leads to a somatic activating mutation of TSH receptors.[4] A single nodule is called a toxic adenoma (Plummer disease).

In contrast with these three disorders, painless or transient (silent) thyroiditis causes a destruction of thyroid follicles via an autoimmune mechanism and a release of preformed thyroid hormones into the circulation.[5] Its clinical presentation is the same as with other causes. In a Danish study, its prevalence among patients with thyrotoxicosis was 0.5%, as evaluated by scintigraphy.[6] Painless thyroiditis can be triggered by childbirth (postpartum thyroiditis) or by use of medications such as lithium, interferon alfa, interleukin-2, and amiodarone.[7]

Gestational hyperthyroidism develops in the first trimester of pregnancy as a result of the stimulatory action of placental beta human chorionic gonadotropin (β-hCG), which shares structural features with TSH, on the thyroid gland.[8] β-hCG-mediated hyperthyroidism can occasionally be caused by hyperemesis gravidarum and, rarely, by a gestational trophoblastic tumor.[8]

Other rare causes of hyperthyroidism are TSH-secreting pituitary adenoma, metastatic follicular thyroid cancer, and struma ovarii.[9]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
The choice of treatment modality for hyperthyroidism caused by overproduction of thyroid hormones depends on the patient's age, symptoms, comorbidities, and preference.	C	25, 26
The diagnostic workup for hyperthyroidism includes measuring thyroid-stimulating hormone, free thyroxine (T_4), and total triiodothyronine (T_3) levels to determine the presence and severity of the condition, as well as radioactive iodine uptake and scan of the thyroid gland to determine the cause.	C	20, 21
Methimazole (Tapazole) is the preferred antithyroid medication except in the first trimester of pregnancy and in patients with an adverse reaction to the medication.	B	26

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

Table 1. Etiology and Pathogenesis of Hyperthyroidism

Etiology	*Mechanism*
Most common causes	
Graves disease	Autoimmune process in which antibodies stimulate the TSH receptor leading to overproduction of thyroid hormones
Painless or transient (silent) thyroiditis	Autoimmune destruction of thyroid tissue leading to a release of preformed thyroid hormones
Toxic adenoma (Plummer disease)	Somatic mutation in TSH receptor or Gs alpha gene in a thyroid nodule
Toxic multinodular goiter	Expansion of clonogenic cells with an activating TSH receptor mutation
Less common causes	
Drug-induced thyroiditis	Overproduction of thyroid hormones (amiodarone-induced thyrotoxicosis type 1) or release of preformed thyroid hormones (amiodarone-induced thyrotoxicosis type 2, interferon alfa, interleukin-2, or lithium)
Hyperemesis gravidarum	High level of β-hCG stimulates TSH receptors
Postpartum thyroiditis	Variant of painless thyroiditis with the same mechanism, occurring after delivery
Subacute granulomatous (de Quervain) thyroiditis	Painful inflammation of the thyroid gland caused by viral infection, often with fever, triggering a release of preformed thyroid hormones
Rare causes	
Factitious thyrotoxicosis	Surreptitious ingestion of thyroid hormones
Metastatic follicular thyroid cancer	Metastasis of functional follicular thyroid cancer
Struma ovarii	Ectopic thyroid tissue in ovarian dermoid tumor produces thyroid hormones
Trophoblastic tumor or a germ cell tumor	Tumor produces β-hCG, which stimulates thyroid TSH receptors
TSH-secreting pituitary adenoma	Tumor secreting large quantities of TSH, and not responding to thyroxine and triiodothyronine feedback

β-hCG = beta human chorionic gonadotropin; TSH = thyroid-stimulating hormone.

Information from references 1 through 9.

Clinical Manifestations

The clinical presentation of hyperthyroidism ranges from asymptomatic to thyroid storm *(Table 2)*.[10-18] Elevated thyroid hormone levels amplify catecholamine signaling through increased numbers of cell surface beta-adrenergic receptors. The resulting adrenergic symptoms (e.g., palpitations, heat intolerance, diaphoresis, tremor, stare [an appearance of a fixed look due to retraction of eyelids], lid lag, hyperdefecation) are the most common manifestations of hyperthyroidism.[10] Hypermetabolism induces weight loss despite an increased appetite. Neuromuscular symptoms include weakness of proximal muscles.[11] Psychiatric symptoms range from anxiety to frank psychosis.[12] Patients with long-standing untreated hyperthyroidism may develop atrial fibrillation (10% to 15% of patients[13,14]) or heart failure (5.8% of patients[15]).

Signs that are pathognomonic for Graves disease include orbitopathy, pretibial myxedema (thyroid dermopathy), and thyroid acropachy, which occur in 25%, 1.5%, and 0.3% of patients, respectively.[16] Goiters that develop in Graves disease are usually smooth and may have a thrill on palpation or a bruit on auscultation. Single or multiple nodules on palpation raise suspicion for a toxic adenoma or a toxic multinodular goiter, although nonfunctioning thyroid nodules may coexist with a goiter in Graves disease.[16]

Graves orbitopathy manifests as exophthalmos or periorbital edema, and it can trigger photophobia, excessive lacrimation,

increased eye sensitivity to wind or smoke, or a sensation of a foreign body in the eyes. In severe cases, blurred vision, diplopia, or reduced color perception may develop.[16] Smoking increases the risk of developing Graves orbitopathy (odds ratio = 3.7).[17]

Pretibial myxedema, a less common finding, develops from fibroblast activation and manifests as swelling over the tibiae with the skin assuming a peau d'orange (orange peel) appearance.[18] Thyroid acropachy, an uncommon sign, is the clubbing of fingers and toes with soft-tissue swelling of the hands and feet.[19] Other skin manifestations of Graves disease include patchy hyperpigmentation and vitiligo.[19]

Laboratory and Radiographic Assessment

Clinical suspicion of hyperthyroidism should prompt laboratory testing *(Figure 1[20-23])*. Some physicians first order a TSH test, which has the highest sensitivity and specificity for hyperthyroidism, and then subsequently obtain free thyroxine (T_4) and total triiodothyronine (T_3) levels (free T_3 assays are poorly validated[1]) if the TSH level is low. Others prefer to order all three tests if hyperthyroidism is suspected to make the diagnosis more efficiently. Many laboratories perform reflex free T_4 testing if TSH is suppressed. *Table 3* lists patterns of thyroid function tests in hyperthyroidism.[20,21] The serum level of thyroid-stimulating immunoglobulins or TSH-receptor antibodies helps distinguish Graves disease from other causes of hyperthyroidism in patients who lack signs pathognomonic of Graves disease and have a contraindication to radioactive iodine uptake and scan.

THYROID FUNCTION TEST RESULTS SIMULATING HYPERTHYROIDISM

Excess estrogen from pregnancy or estrogen therapy leads to elevated levels of thyroxine-binding globulin, which manifests as elevated total T_4 and T_3 levels while TSH and free T_4 levels remain normal *(Table 3)*.[20,21] These findings do not indicate hyperthyroidism and require no treatment.[21]

Patients with critical or acute illness often develop the nonthyroidal illness syndrome manifesting as mildly decreased TSH levels (0.1 to 0.4 mIU per mL) and normal or mildly decreased T_4 levels. In contrast to subclinical hyperthyroidism, the T_3 level is usually low and the reverse T_3 level is elevated. This condition resolves spontaneously when the patient recovers from the acute illness.[21]

Exogenous glucocorticoids or dopamine may cause a mild decrease of TSH levels, a situation often occurring in the intensive care unit. Total T_4, total T_3, and free T_4 levels remain normal. TSH levels return to normal after these medications are discontinued.[21]

RADIOACTIVE IODINE UPTAKE AND THYROID SCAN

A radioactive iodine uptake test and thyroid scan help determine the cause of hyperthyroidism *(Table 4)*. Uptake is the percentage of an iodine 123 (I-123) tracer dose taken up by the thyroid gland, ranging from 15% to 25% at 24 hours. The uptake is very low (0% to 2%) in patients with thyroiditis and high in patients with Graves disease, a toxic adenoma, or a toxic multinodular goiter.[23,24]

The thyroid scan shows the distribution of radiotracer in the gland. A homogeneous distribution indicates Graves disease, but accumulation of I-123 in one area points to

Table 2. Signs and Symptoms of Hyperthyroidism

Adrenergic
Palpitations, tachycardia, anxiety, tremor, jitteriness, diaphoresis, heat intolerance, stare, lid lag, hyperdefecation (not diarrhea)
Cardiovascular
Tachycardia, irregular pulse (in atrial fibrillation), dyspnea, orthopnea and peripheral edema (in heart failure)
Cutaneous
Onycholysis (Plummer nails), patchy or generalized hyperpigmentation (especially of the face and neck)
Symptoms pathognomonic for Graves disease: pretibial myxedema (thyroid dermopathy) and thyroid acropachy (clubbing of fingers and toes accompanied by soft-tissue swelling of the hands and feet)
Patchy vitiligo can also be observed in Graves disease
Hypermetabolism
Weight loss in spite of increased appetite, fever (in thyroid storm)
Neuromuscular
Brisk peripheral reflexes with accelerated relaxation phase and weakness of proximal muscles
Neuropsychiatric
Anxiety, rapid and pressured speech, insomnia, psychosis (if hyperthyroidism is severe)
Ocular
Increased lacrimation, incomplete closure of the eyes when sleeping reported by the patient's partner, photophobia, increased eye sensitivity to wind or smoke, grittiness or sensation of a foreign body or sand in the eyes
Symptoms pathognomonic for Graves disease: exophthalmos, periorbital edema, diplopia, blurred vision, reduced color perception

Information from references 10 through 18.

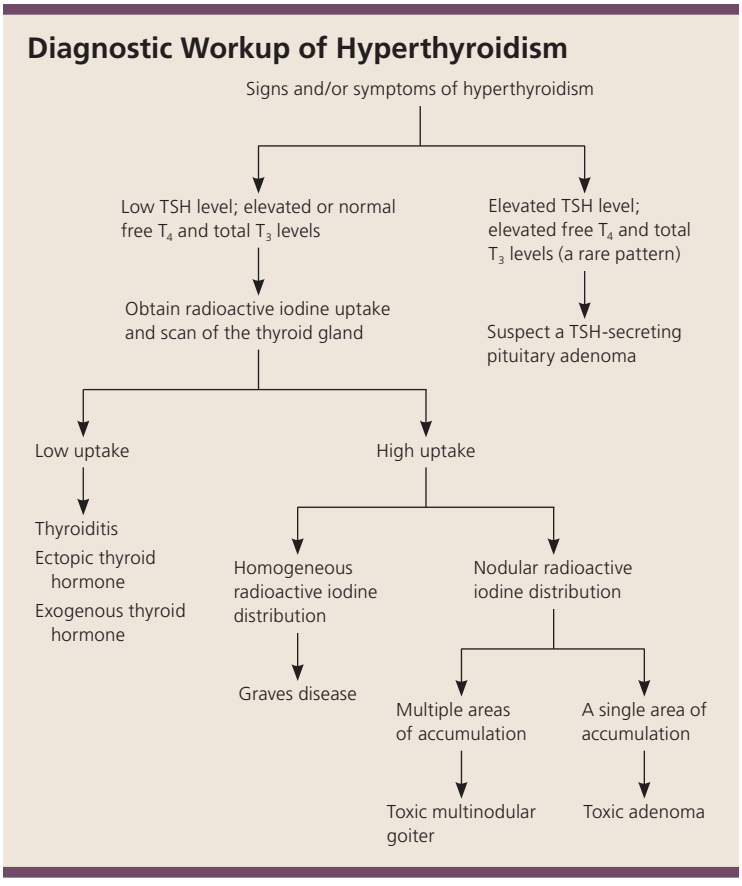

Figure 1. Algorithm for the diagnostic workup of hyperthyroidism. (T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.)

Information from references 20 through 23.

a toxic adenoma *(Figure 2)* or in multiple areas to a toxic multinodular goiter.[23,24]

Ultrasonography is sometimes used as a cost-effective and safe alternative to radioactive iodine uptake and scan. It is the primary imaging modality used during pregnancy, lactation, and in amiodarone-induced thyrotoxicosis.[24]

Treatment

Regardless of the cause of hyperthyroidism, the adrenergic symptoms are controlled by beta blockers *(Table 5)*.[25-28] Propranolol has the theoretical advantage of also inhibiting 5'-monodeiodinase, thus blocking peripheral conversion of T_4 to T_3.[25] The choice of treatment modality for hyperthyroidism caused by overproduction of thyroid hormones depends on the patient's age, symptoms, comorbidities, and preference.[25,26]

GRAVES DISEASE

Graves disease requires one of the three treatment options: an antithyroid medication (methimazole [Tapazole] or propylthiouracil), radioactive iodine (I-131) ablation of the thyroid gland, or surgical thyroidectomy. The choice of treatment depends on the benefits vs. risks in a specific clinical situation and on the patient's preference[25] *(eTable A)*.

Antithyroid Medications. Antithyroid medications are thionamides; they inhibit thyroid peroxidase, blocking the synthesis of T_3 and T_4. Thionamides can serve as a long-term therapy or as a bridge to I-131 ablation or thyroidectomy, with the goal of normalizing thyroid function and preventing exacerbation of hyperthyroidism after I-131 ablation or avoiding surgical risks associated with uncontrolled

Table 3. Thyroid Function Test Results in Hyperthyroidism and in Conditions Simulating Hyperthyroidism

Condition	*TSH*	*Total T_4*	*Free T_4*	*Total T_3*
Overt hyperthyroidism	Suppressed	Elevated	Elevated	Elevated
Subclinical hyperthyroidism*	Suppressed or low	Normal	Normal	Normal
TSH-secreting pituitary adenoma	Normal or elevated	Elevated	Elevated	Elevated
Estrogen excess	Normal	Elevated	Normal	Elevated
Nonthyroidal illness syndrome	Low	Normal or mildly decreased	Normal	Low (and reverse T_3 is elevated)
Glucocorticoid and/or dopamine therapy	Low	Normal	Normal	Normal

NOTE: *Suppressed TSH is < 0.1 mIU per mL; low TSH is 0.1 to 0.4 mIU per mL.*

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

**—Subclinical hyperthyroidism does not refer to the absence of signs and symptoms.*

Information from references 20 and 21.

Table 4. Patterns Observed in Radioactive Iodine Uptake and Scan

Condition	*Radioactive iodine uptake (normal = 15% to 25%)*	*Radiotracer distribution in the thyroid gland*
Graves disease	High	Homogeneous
Toxic adenoma	High	Iodine 123 is concentrated in one spot
Toxic multinodular goiter	High	Iodine 123 is concentrated in multiple spots
Thyroiditis	Low	Not applicable

hyperthyroidism. Because Graves disease remits in up to 30% of patients treated with thionamides, these medications can be used as the initial treatment, with ablation or thyroidectomy performed if remission does not occur.[25,26] Once medical therapy is discontinued, relapse occurs in 30% to 70% of patients, mostly within the first year.[27] After discontinuation, thyroid function should be monitored every one to three months for six to 12 months, and the patient should be instructed to contact the physician if symptoms recur.

Because use of propylthiouracil has a higher risk of causing severe liver injury, as highlighted in the U.S. Food and Drug Administration's boxed warning, methimazole is preferred except during the first trimester of pregnancy (can cause birth defects) and in patients with an adverse reaction to methimazole.[28,29] For patients using methimazole, the prevalence of agranulocytosis is 0.17%, the incidence of hepatitis is 3.17 per 1,000 person-years, and the incidence of acute hepatic failure is 0.32 per 1,000 person-years.[30,31] Patients should be instructed to discontinue medication use and contact their physician if they develop jaundice, acholic stools, dark urine, arthralgias, abdominal pain, nausea, vomiting, fever, or sore throat. A baseline complete blood count (CBC) with differential and a hepatic panel should be obtained before initiating an antithyroid medication. Subsequent routine monitoring of CBC is unnecessary, but CBC with differential should be obtained if fever and/or pharyngitis develop.

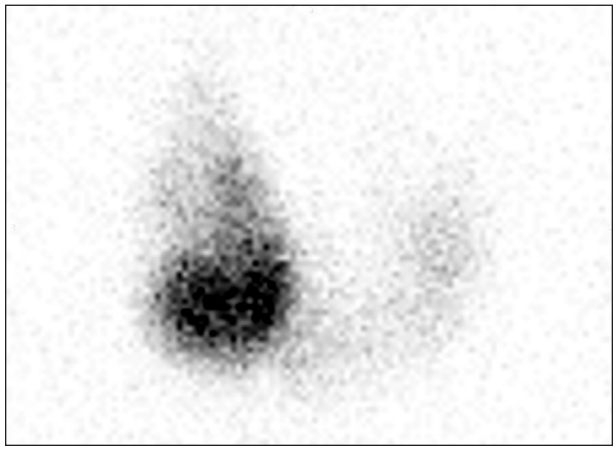

Figure 2. Toxic adenoma on radioactive iodine scan.

Free T_4 and total T_3 should be obtained four weeks after starting a thionamide and every four to eight weeks thereafter with the dosage adjusted based on results. Once free T_4 and total T_3 levels normalize, they should be monitored every three months. Serum TSH is of limited value early in the treatment course because levels may remain suppressed for several months after treatment is started. An antithyroid medication should be continued for 12 to 18 months, then tapered or discontinued if the TSH level is normal at the time. Elevated or above-normal TSH levels (greater than 4.0 mIU per mL) at antithyroid drug discontinuation is associated with an increased likelihood of permanent remission.[27]

Radioactive Iodine Ablation. Radioactive iodine ablation of the thyroid gland is the most common treatment of Graves disease in the United States. It is contraindicated in pregnancy. Moderate to severe Graves orbitopathy is a relative contraindication, especially in patients who smoke, because radioactive iodine may exacerbate the eye disease.[32,33] In mild cases of Graves orbitopathy, radioactive iodine ablation can be performed with concomitant glucocorticoid therapy. Nonradioactive iodine impedes radioactive iodine uptake by iodide transporter; therefore, exposure to large amounts of nonradioactive iodine (e.g., iodinated contrast, amiodarone) should be avoided within three months before radioactive iodine ablation. Pregnancy should be ruled out within 48 hours before radioactive iodine ablation and avoided for six months thereafter.[1] A thionamide should be discontinued at least five days before the treatment but can be restarted three to five days after to maintain control of thyroid function, because it may take up to 12 weeks to achieve the full effect of radioactive iodine.

Most patients develop permanent hypothyroidism between two and six months after radioactive iodine ablation and require thyroid hormone supplementation.[1,33] Free T_4 and total T_3 should be measured four to eight weeks after ablation; if hyperthyroidism persists, these indices should be monitored every four to six weeks and thyroid hormone replacement started in the early stages of hypothyroidism.[1]

Table 5. Pharmacologic Treatment of Hyperthyroidism

First-line agents	*Dosage*	*Adverse effects*	*Comments*	*Cost**
Beta blockers				
Atenolol	25 to 100 mg orally once per day	Exacerbation of congestive heart failure	Selective beta$_1$ blocker; safer than propranolol in asthma or chronic obstructive pulmonary disease; once-daily dosing improves compliance	$5
Propranolol	Immediate release: 10 to 40 mg orally every eight hours Extended release: 80 to 160 mg orally once per day	Exacerbation of congestive heart failure or asthma	Decreases T_4 to T_3 conversion; nonselective beta blocker	$20 to $84 for immediate release $76 to $152 for extended release
Antithyroid medications				
Methimazole (Tapazole)	5 to 120 mg orally per day (can be given in divided doses)	Dose-related agranulocytosis	Contraindicated in the first trimester of pregnancy	$20 to $100 ($45 to $900)
Propylthiouracil	50 to 300 mg orally every eight hours	Agranulocytosis not related to dose; liver dysfunction; rash, including ANCA-associated vasculitis	Drug of choice in the first trimester of pregnancy; carries a higher risk of liver failure than methimazole	$60 to $400
Radioactive iodine	Usually 10 to 30 millicurie, depending on uptake and the size of the thyroid gland	May aggravate hyperthyroidism in the early posttreatment period Causes hypothyroidism three to six months after treatment	Contraindicated in severe Graves orbitopathy and in patients who are pregnant or nursing	—
Ancillary agents				
Cholestyramine	1 to 2 g orally twice per day	Constipation or diarrhea; bloating	Binds thyroid hormones in the intestine and thus increases fecal excretion	$50
Glucocorticoids	Prednisone: 20 to 40 mg orally per day for up to four weeks Hydrocortisone: 100 mg intravenously every eight hours with subsequent taper	Hyperglycemia in patients with diabetes mellitus, otherwise few short-term adverse effects	Used in severe hyperthyroidism or thyroid storm to reduce T_4 to T_3 conversion; also used in severe subacute thyroiditis	Prednisone: $20 Hydrocortisone: NA
Nonsteroidal anti-inflammatory drugs	Depends on the specific agent	Nephrotoxicity; gastrointestinal bleeding	Treats pain in subacute thyroiditis	—
Supersaturated potassium iodide	5 drops orally every eight hours	May aggravate hyperthyroidism if given before an antithyroid agent	Give at least one hour after methimazole or propylthiouracil Do not give before radioactive iodine treatment	—

ANCA = antineutrophil cytoplasmic autoantibodies; NA = not applicable; T_3 = triiodothyronine; T_4 = thyroxine.

**—Estimated retail price of one month's treatment based on information obtained at http://www.goodrx.com (accessed November 11, 2015). Generic price listed first; brand price listed in parentheses.*

Information from references 25 through 28.

Thyroidectomy. This treatment option is preferred in patients with goiter-induced compressive symptoms and in patients with contraindications to radioactive iodine ablation or thionamides. Besides general anesthesia risk, thyroidectomy carries a risk of inadvertently injuring parathyroid glands and recurrent laryngeal nerves.[34]

TOXIC ADENOMA OR TOXIC MULTINODULAR GOITER

Antithyroid medications can control hyperthyroidism, but do not induce remission of hyperthyroidism associated with toxic adenoma or toxic multinodular goiter. Therefore, radioactive iodine ablation and thyroidectomy are the main treatment options for these

BEST PRACTICES IN ENDOCRINOLOGY: RECOMMENDATIONS FROM THE CHOOSING WISELY CAMPAIGN

Recommendation	*Sponsoring organization*
Do not order multiple tests in the initial evaluation of a patient with suspected thyroid disease. Order TSH, and if abnormal, follow up with additional evaluation or treatment depending on the findings.	American Society for Clinical Pathology
Do not routinely order a thyroid ultrasound in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland.	The Endocrine Society/American Association of Clinical Endocrinologists

TSH = thyroid-stimulating hormone.

Source: For more information on the Choosing Wisely Campaign, see http://www.choosingwisely.org. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see http://www.aafp.org/afp/recommendations/search.htm.

conditions. Thyroidectomy is favored if a nodule or goiter causes compressive symptoms. Antithyroid medications may be used for long-term treatment in select patients who refuse ablation or who have a contraindication to thyroidectomy.[35,36]

THYROIDITIS

Painless thyroiditis and subacute thyroiditis are self-limiting conditions that usually resolve spontaneously within six months. There is no role for antithyroid medications or radioactive iodine ablation in the treatment of thyroiditis. Beta blockers may be used if needed to control adrenergic symptoms. Pain associated with subacute thyroiditis may be relieved with a nonsteroidal anti-inflammatory drug.[5]

THYROID STORM

Graves disease, toxic adenoma, and toxic multinodular goiter can sometimes cause severe hyperthyroidism, which is termed a thyroid storm. The Burch-Wartofsky score is a helpful tool for diagnosing thyroid storm[37] *(eTable B)*. Treatment of thyroid storm is summarized in *eTable C*.

DRUG-ASSOCIATED HYPERTHYROIDISM

Amiodarone-induced thyrotoxicosis can be classified as type 1 (thyroid hormone overproduction, treated with antithyroid medications) or type 2 (thyroid tissue destruction, treated with steroids). Amiodarone should not be discontinued unless it can be stopped safely, without triggering cardiac complications.[38,39]

Hyperthyroidism associated with use of other medications (e.g., lithium, interferon alfa, tyrosine kinase inhibitors, highly active antiretroviral therapy) is usually self-limited. The physician should determine whether the medication may be discontinued safely or replaced with a different medication.

Data Sources: A PubMed search was performed in Clinical Queries using the key terms hyperthyroidism, thyrotoxicosis, Graves disease, toxic multinodular goiter, toxic adenoma, and thyroiditis. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. Also searched were Essential Evidence Plus, the Cochrane database, the National Guideline Clearinghouse database, and UpToDate. Search dates: December 26, 2014, and August 24, 2015.

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eTable A. Benefits and Risks of Graves Disease Treatment Options

Treatment options	*Benefits*	*Risks*
Antithyroid medication (methimazole [Tapazole] or propylthiouracil)	No exposure to radiation or to surgical risks No permanent hypothyroidism Propylthiouracil is safe for the fetus in the first trimester of pregnancy	Agranulocytosis, hepatotoxicity (especially with propylthiouracil), rash Methimazole can cause aplasia cutis and other birth defects in the first trimester of pregnancy
Radioactive iodine ablation	No exposure to potential adverse effects of an antithyroid medication or to surgical risks Treatment of choice in the United States	Aggravation of Graves orbitopathy, especially in smokers Permanent hypothyroidism (occurs in most patients) Radiation exposure Failure to cure hyperthyroidism if the radioactive iodine dose is insufficient Risk of Graves disease recurrence even after successful treatment Contraindicated in pregnancy
Thyroidectomy	No exposure to adverse effects of an antithyroid medication or to radiation Little chance of Graves disease recurrence	Risk of general anesthesia Risk of damaging recurrent laryngeal nerve leading to hoarse voice (if damage is unilateral) or of respiratory distress (if damage is bilateral) Risk of inadvertent damage or removal of parathyroid glands leading to permanent hypoparathyroidism

Information from:

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eTable B. Burch-Wartofsky Score: Diagnostic Criteria for Thyroid Storm

Criteria	*Score*
Thermoregulatory dysfunction	
Temperature (°F)	
99 to 99.9	5
100 to 100.9	10
101 to 101.9	15
102 to 102.9	20
103 to 103.9	25
≥ 104	30
Central nervous system effects	
Absent	0
Mild	10
Agitation	
Moderate	20
Delirium	
Psychosis	
Extreme lethargy	
Severe	30
Seizure	
Coma	
Gastrointestinal-hepatic dysfunction	
Absent	0
Moderate	10
Diarrhea	
Nausea/vomiting	
Abdominal pain	
Severe	20
Unexplained jaundice	

Criteria	*Score*
Cardiovascular dysfunction	
Tachycardia (bpm)	
90 to 109	5
110 to 119	10
120 to 129	15
130 to 139	20
≥ 140	25
Congestive heart failure	
Absent	0
Mild	5
Pedal edema	
Moderate	10
Bibasilar rales	
Severe	15
Pulmonary edema	
Atrial fibrillation	
Absent	0
Present	10
Precipitant history	
Negative	0
Positive	10

bpm = beats per minute.

NOTE: *A score of 45 or greater is highly suggestive of thyroid storm, a score of 25 to 44 is suggestive of impending storm, and a score below 25 is unlikely to represent thyroid storm.*

Adapted with permission from Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am. *1993;22(2):266.*

eTable C. Treatment of Thyroid Storm

Supportive treatment
Airway maintenance
Oxygen
IV fluids
Cooling blanket (do not use salicylate to treat fever because salicylates increase free T_4 and free T_3 levels)
Inhibit T_4 and T_3 synthesis
Methimazole (Tapazole) orally, rectally, via nasogastric tube, or IV, 20 to 40 mg every eight hours
Propylthiouracil orally, rectally, or via nasogastric tube, 200 to 400 mg every eight hours
Inhibit T_4 and T_3 release
Saturated solution of potassium iodide, five drops orally every six hours to be started at least one hour after administration of an antithyroid agent
Heart rate control
Esmolol (Brevibloc) IV, 50 to 100 mcg per kg per minute
Propranolol, 60 to 80 mg orally every four hours
Metoprolol IV, 5 to 10 mg every two to four hours
If beta-blockade is contraindicated, use diltiazem IV, 0.25 mg per kg over two minutes, then 10 mg per hour IV infusion or 60 to 90 mg orally every six to eight hours
Inhibit T_4 to T_3 conversion
Hydrocortisone 100 mg IV every eight hours (also suppresses autoimmune process in Graves disease)
Treat precipitating cause

IV = intravenous; T_3 = triiodothyronine; T_4 = thyroxine.

Information from Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am. *2006;35(4):663-686, vii.*