Annals of Internal Medicine®

In the Clinic®

Hyperthyroidism

Screening

Diagnosis

Treatment

Practice Improvement

Thyrotoxicosis is a general term for excess circulating and tissue thyroid hormone levels, whereas *hyperthyroidism* specifically denotes disorders involving a hyperactive thyroid gland (Graves disease, toxic multinodular goiter, toxic adenoma). Diagnosis and determination of the cause rely on clinical evaluation, laboratory tests, and imaging studies. Hyperthyroidism is treated with antithyroid drugs, radioactive iodine ablation, or thyroidectomy. Other types of thyrotoxicosis are monitored and treated with β-blockers to control symptoms given that most of these conditions resolve spontaneously.

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Thyrotoxicosis is a clinical state characterized by excess serum and tissue concentrations of thyroxine (T_4), triiodothyronine (T_3), or both. The term *hyperthyroidism* refers specifically to thyrotoxicosis resulting from hyperactivity of the thyroid gland. Thyrotoxicosis is considered "overt" when the serum thyroid-stimulating hormone (TSH) level is low or undetectable and serum T_4 (free or total T_4) level, total T_3 level, or both are above the reference range, and it is considered "subclinical" when the TSH level is low or undetectable but levels of both T_4 (free or total T_4) and total T_3 are within the reference range. Therefore, overt and subclinical thyrotoxicosis are defined biochemically without regard for clinical features. The prevalence of thyrotoxicosis in the United States is estimated at 1.2%, with approximately 40% of cases being overt and 60% being subclinical (1).

Screening

Who has elevated risk for thyrotoxicosis?

Persons at increased risk for thyrotoxicosis include those with goiters, type 1 diabetes, other autoimmune diseases, and a family history of thyroid disease. Medications that increase risk include amiodarone, interferon-α, interleukin-2, lithium, iodide, iodinated contrast agents, immune checkpoint inhibitors, and alemtuzumab (2–5).

Should clinicians screen for thyrotoxicosis?

Screening in the general population is not cost-effective because of the low prevalence of thyrotoxicosis (6). However, case finding is recommended in persons who are at high risk because of comorbid conditions, family history, or medication use. Testing should also be considered in patients with medical conditions that may be caused or aggravated by thyrotoxicosis (osteoporosis, atrial fibrillation, supraventricular tachycardia, or heart failure). Screening is also recommended in women older than 50 years (6) because of the higher prevalence of thyroid disease in this group.

What screening tests should be used?

Serum TSH measurement is the best test for thyrotoxicosis. TSH is undetectable or low in both overt and subclinical thyrotoxicosis because of negative feedback by elevated or high normal T_4 and/or T_3 levels on the pituitary gland. TSH assays are standardized, accurate, and widely available.

Screening... Screening for thyrotoxicosis in the general population is not cost-effective. Experts recommend measuring serum TSH levels in persons with goiters, type 1 diabetes, other autoimmune diseases, osteoporosis, atrial fibrillation, supraventricular tachycardia, heart failure, or a family history of thyroid disease; those taking amiodarone, immune checkpoint inhibitors, or alemtuzumab; and women older than 50 years.

CLINICAL BOTTOM LINE

What symptoms should prompt clinicians to consider thyrotoxicosis or hyperthyroidism?

Symptoms that suggest thyrotoxicosis include nervousness, increased sweating, heat intolerance, palpitations, fatigue, weight loss, tachycardia, dyspnea, weakness, leg edema, eye symptoms, emotional lability, and frequent defecation (7–9). Elderly patients tend to have milder, more subtle, and less typical symptoms that are often dominated by fatigue, depression, weight loss, and atrial fibrillation (7–10); the term *apathetic thyrotoxicosis* describes this presentation.

Some elements of the history may also suggest the specific cause of thyrotoxicosis (**Appendix Table 1**, available at Annals.org). Eye pain or swelling, double vision, or a skin disorder on the shins point to Graves disease as the cause (1, 11). Recent pregnancy raises the possibility of postpartum thyroiditis. Anterior neck pain, malaise, fever, and sore throat are characteristic of subacute thyroiditis. Use of amiodarone, lithium, interferon-α, interleukin-2, potassium iodide, immune checkpoint inhibitors (especially ipilimumab and nivolumab) (3, 4), or alemtuzumab (5) or recent exposure to iodinated radiocontrast agents increase the likelihood of drug-induced or iodine-induced thyrotoxicosis (2). Surreptitious ingestion of thyroid hormone must also be considered.

What physical examination findings indicate possible thyrotoxicosis or hyperthyroidism?

Physical signs often identified with thyrotoxicosis of any cause include tachycardia and/or an irregularly irregular heart rate; goiter; warm, moist skin; hand tremor; and adrenergic eye signs (stare and lid lag) (**Appendix Table 1**) (7–9). Other features may indicate the specific cause. Graves disease is characterized by diffuse goiter, thyroid bruit, inflammatory/congestive eye signs (proptosis, periorbital edema, chemosis, extraocular muscle dysfunction), pretibial myxedema (usually on the shins), and thyroid acropachy (soft tissue enlargement and clubbing of the fingers) (1, 11). The diagnosis of toxic multinodular goiter or toxic adenoma is supported by palpating multiple thyroid nodules or a solitary nodule. Fever and thyroid tenderness suggest subacute thyroiditis (12).

What laboratory tests should clinicians use to diagnose thyrotoxicosis or hyperthyroidism?

Serum TSH measurement is the best test for diagnosis of thyrotoxicosis. Levels are usually undetectable in overt thyrotoxicosis and low but often detectable in subclinical thyrotoxicosis. Either should prompt the clinician to order a free T_4 or total T_4 (if free T_4 is not available) test. If the free or total T_4 level is normal, a total T_3 test should be ordered because some patients have normal T_4 levels but elevated T_3 levels (T_3 toxicosis). Measurement of free T_3 levels is not recommended because of inaccuracy of the available assays.

Once thyrotoxicosis is diagnosed, the cause must be determined. When the physical examination strongly suggests Graves disease (diffuse goiter, thyroid bruit, thyroid orbitopathy [inflammatory/congestive eye signs], pretibial myxedema, thyroid

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Table 1. **Laboratory and Other Studies for Thyrotoxicosis**

Test	*Indication*
TSH	Suspected thyrotoxicosis
Free T_4	Suppressed TSH
Total T_3	Suppressed TSH; normal free T_4 level
Thyroglobulin	Suspected thyroiditis (subacute, postpartum, or silent)
Erythrocyte sedimentation rate	Suspected subacute thyroiditis
TRAb	Thyrotoxicosis differential diagnosis (positive in Graves disease) Euthyroid Graves orbitopathy Assessment of remission during antithyroid drug therapy in Graves disease Assessment of neonatal risk in pregnant patients with Graves disease
Thyroid peroxidase antibodies	Confirmation of Hashimoto thyroiditis and autoimmune thyroid disease in general (including Graves disease) Assessment of risk for drug-induced thyroid dysfunction and postpartum or silent thyroiditis
Thyroid hormone antibodies (anti-T_4 and anti-T_3 antibodies)	Investigation of incongruous thyroid hormone and TSH results (spuriously high free T_4 and total T_3) in patients with Hashimoto thyroiditis
RAIU	Confirmed biochemical thyrotoxicosis with negative TRAb level or palpable thyroid nodules
Thyroid scan	Confirmed biochemical thyrotoxicosis; normal or elevated RAIU
Thyroid ultrasonography	Presence of thyroid nodules; differentiation of type 1 (iodine-induced) and type 2 (thyroiditis) amiodarone-induced thyrotoxicosis
Color Doppler ultrasonography	Differentiation of type 1 and type 2 amiodarone-induced thyrotoxicosis
Whole-body scan	Suspected struma ovarii or functioning metastatic follicular carcinoma
Human chorionic gonadotropin	Confirmation of pregnancy, gestational thyrotoxicosis, hyperemesis gravidarum, choriocarcinoma, molar pregnancy, testicular tumor

RAIU = radioactive iodine uptake; TRAb = thyrotropin receptor antibody; TSH = thyroid-stimulating hormone.

acropachy), further testing is unnecessary (1, 11). However, if the cause is unclear, additional testing is needed because treatment differs considerably for specific causes (**Tables 1** and **2**; also see the Box: Differential Diagnosis of Thyrotoxicosis With the Use of RAIU Test). Measurement of serum thyrotropin receptor antibodies (TRAbs) is recommended if thyroid palpation does not identify thyroid nodules or significant tenderness (1, 11–13). If TRAb levels are positive, the diagnosis is usually Graves disease and no further tests are needed; TRAbs have sensitivity of 96%–97% and specificity of 99% for Graves disease (11) but can be weakly positive in subacute thyroiditis. If thyroid nodules are present or if TRAb levels are negative or borderline positive, a radioactive iodine uptake (RAIU) test and a thyroid scan should be ordered (1).

Hyperthyroidism (thyrotoxicosis with high or normal RAIU) usually results from 1 of 3 disorders: Graves disease, toxic multinodular goiter, or toxic thyroid adenoma (Box: Differential Diagnosis of Thyrotoxicosis With the Use of RAIU Test). The thyroid scan distinguishes among these 3 conditions (1). Diffuse isotope uptake is seen in Graves disease, patchy uptake (multiple nodules) is seen with toxic multinodular goiter, and uptake in a single nodule with suppression of the remainder of the thyroid gland is seen with toxic adenoma.

Table 2. **Differential Diagnosis of Thyrotoxicosis**

Disease	*Characteristics*	*Reference*
Elevated free T_4 level, suppressed TSH		
Graves disease	Positive TRAb level; increased/normal RAIU; homogeneous thyroid scan	1, 11
Toxic multinodular goiter	Increased/normal RAIU; heterogeneous thyroid scan	1
Toxic thyroid adenoma	Increased/normal RAIU; single "hot" focus on thyroid scan with suppression of remainder of thyroid	1
Subacute thyroiditis	Low RAIU; no visible uptake on thyroid scan; increased erythrocyte sedimentation rate; high thyroglobulin level; may be followed by hypothyroid phase	1, 12
Postpartum or silent thyroiditis	Low RAIU; no visible uptake on thyroid scan; high thyroglobulin level; may be followed by hypothyroid phase	1
Surreptitious/iatrogenic thyroid hormone ingestion	Low RAIU and thyroglobulin level; may involve L-thyroxine or liothyronine ingestion	1
Checkpoint inhibitor therapy	History of checkpoint inhibitor use; RAIU may be high, normal, or low	2–4
Alemtuzumab	History of alemtuzumab use; RAIU usually high; homogeneous thyroid scan	2, 5
Struma ovarii	Low RAIU in neck; increased pelvic uptake on whole-body scan	1
TSH-producing pituitary tumor	Normal or high TSH level; increased/normal RAIU; elevated α-subunit level; pituitary tumor present on magnetic resonance imaging	1
Gestational thyrotoxicosis	Increased human chorionic gonadotropin level; negative TRAb level; nuclear medicine testing contraindicated	1
Hyperemesis gravidarum	Increased human chorionic gonadotropin level; negative TRAb level; nuclear medicine testing contraindicated	1
Choriocarcinoma, molar pregnancy, testicular tumor	Increased human chorionic gonadotropin level; negative TRAb level; increased/normal RAIU; homogeneous thyroid scan	1
AIT	Two distinct types of thyrotoxicosis: type 1 AIT (iodine-induced) and type 2 AIT (thyroiditis); negative TRAb level; low RAIU	1
Functional, widely metastatic follicular thyroid cancer	Prior thyroidectomy in most patients; low RAIU in neck; increased uptake in metastases on whole-body scan	1
McCune–Albright syndrome	Negative TRAb level; increased/normal RAIU; homogeneous thyroid scan	–
Normal or low free T_4 level, suppressed TSH		
Subclinical thyrotoxicosis	Normal free T_4 level; RAIU may be high or normal	1, 43
Recent thyrotoxicosis	After treatment for hyperthyroidism	1, 43
Normal pregnancy	Increased human chorionic gonadotropin level; negative TRAb level; nuclear medicine testing contraindicated	1, 43
Central hypothyroidism	TSH level may be low or normal; free T_4 level may be low	1, 43
Recovery from thyroiditis	TSH level may be low, normal, or elevated	1, 12, 43
Nonthyroidal illness	TSH level may be low, normal, or elevated	1
Corticosteroid therapy	Suppressive effect on TSH	2
Dopamine therapy	Suppressive effect on TSH	2
Mitotane therapy	Suppressive effect on TSH; adrenal cancer treatment	2
Bexarotene therapy	Suppressive effect on TSH; mycosis fungoides treatment	2

AIT = amiodarone-induced thyrotoxicosis; RAIU = radioactive iodine uptake; TRAb = thyrotropin receptor antibody; TSH = thyroid-stimulating hormone.

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Differential Diagnosis of Thyrotoxicosis With the Use of RAIU Test

High or normal RAIU (hyperthyroidism)

- Graves disease
- Toxic multinodular goiter
- Toxic thyroid adenoma
- HCG-induced hyperthyroidism
- TSH-producing pituitary tumor
- McCune–Albright syndrome

Low or undetectable RAIU (other types of thyrotoxicosis)

- Silent thyroiditis
- Postpartum thyroiditis
- Subacute (granulomatous) thyroiditis
- Iodine-induced thyrotoxicosis
- Amiodarone-induced thyrotoxicosis
- Iatrogenic thyrotoxicosis
- Metastatic follicular thyroid cancer
- Struma ovarii

HCG = human chorionic gonadotropin; RAIU = radioactive iodine uptake; TSH = thyroid-stimulating hormone.

Other tests that may be considered when TRAb levels are negative and radioisotope studies are contraindicated or not desired (for example, in women who are pregnant or nursing, or due to patient preference) (1) include thyroid ultrasonography with or without color Doppler (1, 13); measurement of serum thyroid-stimulating immunoglobulins, serum thyroid peroxidase antibodies, serum thyroglobulin, serum human chorionic gonadotropin, erythrocyte sedimentation rate, or 24-hour urinary iodine excretion; or (rarely) whole-body radioiodine scan (1).

Amiodarone-induced thyrotoxicosis (AIT) can be particularly difficult to accurately diagnose and treat (14). Type 1 AIT is a form of iodine-induced thyrotoxicosis caused by the high iodine content in amiodarone; it typically occurs in patients with underlying nodular thyroid disease. Type 2 AIT is a form of amiodarone-induced thyroiditis. Findings that suggest type 1 AIT include thyroid nodules on examination or ultrasonogram, increased blood flow on color Doppler, and low but detectable RAIU. Findings that indicate probable type 2 AIT include normal findings on thyroid examination and ultrasonogram, decreased color Doppler blood flow, absent or very low RAIU, and elevated serum interleukin-6 level (14).

What alternative explanations should clinicians consider in patients with possible thyrotoxicosis?

Clinical features that resemble those of thyrotoxicosis can occur with infections, sepsis, anxiety, depression, chronic fatigue, atrial fibrillation, and pheochromocytoma. Thyroid hormone testing can usually distinguish these disorders from thyrotoxicosis. However, serum TSH levels can be low and free T_4 levels can be variable in normal pregnancy, gestational thyrotoxicosis, hyperemesis gravidarum, nonthyroidal illness syndrome, or central hypothyroidism (hypothalamic–pituitary disease) and with use of some medications, including glucocorticoids, dopamine, bexarotene, mitotane, metformin, and heparin (1, 2).

It is particularly important to note the effects of high-dose biotin use on thyroid tests (2, 15). Biotin is a common supplement in over-the-counter preparations for treatment of hair loss and brittle nails. At the high doses used in these products, biotin can interfere with multiple hormone assays because it is a key reagent used in assays; consequently, excess biotin in the circulation (and thus in the test tube) can alter assay performance and produce false results. For example, high-dose biotin can result in low serum TSH levels, elevated free

T_4 and total T_3 levels, and positive TRAb levels in a euthyroid person, a profile that could be mistaken for hyperthyroid Graves disease. Patients who are taking high-dose biotin supplements should stop 2–3 days before having hormone measurements and can resume taking them afterward if desired (2, 15).

When should clinicians consider consulting an endocrinologist?

Clinicians should consider consulting an endocrinologist when the diagnosis of thyrotoxicosis is uncertain or the cause is unclear, such as when TRAb levels are negative and RAIU is low or undetectable.

Diagnosis... Thyrotoxicosis is diagnosed on the basis of the history, physical examination, and characteristic laboratory findings (low serum TSH level with elevated levels of free T_4 and/or total T_3). Clinicians should identify the cause from clinical features along with TRAb testing, RAIU testing, and thyroid scan, when indicated. In some situations, determining the cause may require additional tests.

CLINICAL BOTTOM LINE

Treatment

What nonpharmacologic therapies should clinicians recommend?

Patients with uncontrolled thyrotoxicosis should avoid strenuous physical exertion; reduce or eliminate caffeine intake; quit smoking (1); avoid exogenous sources of iodine (kelp, iodine supplements, iodinated contrast agents); and avoid biotin supplements, which can interfere with hormone assay accuracy (2, 15).

How should clinicians choose and prescribe drug therapy?

Medications that are available to treat thyrotoxicosis are shown in **Table 3**. β-Adrenergic blockers are appropriate for symptomatic patients with thyrotoxicosis of any cause (1, 16) regardless of the primary therapy chosen for the condition.

Methimazole and propylthiouracil (PTU) are the 2 antithyroid drugs (ATDs) available in the United States; carbimazole is used in parts of Europe, Africa, and Asia. ATDs inhibit thyroid hormone synthesis and reduce serum thyroid hormone levels relatively quickly in patients with Graves disease, toxic multinodular goiter, or toxic thyroid adenoma (1, 16–18); they are usually not effective in other types of thyrotoxicosis (1). Methimazole is more potent than PTU (1, 16–18), requires less frequent dosing (once or twice daily), and is preferred because of the higher risk for liver toxicity with PTU (1). The starting dose of methimazole depends on the initial free T_4 level. When free T_4 levels are 1.0–1.5 times the upper limit of normal (ULN), the recommended starting methimazole dose is 5–10 mg once daily; when free T_4 levels are 1.5–2.0 times the ULN, the starting dose is 10–20 mg once daily; and when free T_4 levels are 2.0–3.0 times the ULN or higher, the starting dose is 30–40 mg once daily or in divided twice-daily doses (1, 18).

The recommended duration of methimazole therapy for Graves disease is 12–18 months, after which it can be tapered or discontinued if the patient is

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Table 3. **Drug Treatments for Thyrotoxicosis**

Agent	*Mechanism of Action*	*Dosage*	*Benefits*	*Adverse Effects*	*Notes*
Propranolol	β-Blocker	60–80 mg every 4 h	Blocks T_4-to-T_3 conversion (high doses)	Possible aggravation of heart failure, asthma	In thyroid storm, consider invasive monitoring in patients with heart failure
Atenolol	β-Blocker	50–100 mg every 12–24 h	Once-daily dosing possible	Possible aggravation of heart failure	Uncomplicated thyrotoxicosis only
Metoprolol	β-Blocker	50–100 mg every 12–24 h	Once-daily dosing possible	Possible aggravation of heart failure	Uncomplicated thyrotoxicosis only
Esmolol	β-Blocker	250–500 mcg/kg intravenous loading dose, then continuous infusion of 50–100 mcg/kg per min	Rapidly titratable	Intensive monitoring required	Thyroid storm only; consider invasive monitoring in patients with heart failure
Methimazole	ATD: inhibits thyroid hormone synthesis	Free T_4 level 1.0–1.5 times ULN: Start 5–10 mg once daily Free T_4 level 1.5–2.0 times ULN: Start 10–20 mg once daily Free T_4 level 2.0–3.0 times ULN or higher: Start 30–40 mg once daily or in divided doses twice daily	–	Agranulocytosis (0.2%–0.4%), cholestatic jaundice (<0.2%), birth defects (e.g., aplasia cutis, choanal atresia) if used in first trimester of pregnancy (more common than with PTU)	Delayed effect seen due to preformed thyroid hormone release; thyroid storm dose higher (20 mg every 4 h; PTU preferred) Manufacturer recommends performing liver function tests in the event of anorexia, pruritus, or right upper quadrant abdominal pain and stopping therapy for aminotransferase elevations >3 times ULN Agranulocytosis occurred in 0.2%–0.4% of patients receiving ATDs in 3 studies involving >22 000 patients
PTU	ATD: inhibits thyroid hormone synthesis and T_4-to-T_3 conversion	50–150 mg 3 times daily	Blocks T_4-to-T_3 conversion	Agranulocytosis (0.2%–0.4%), hepatitis (<0.2%), vasculitis, birth defects if used in first trimester of pregnancy (less common than with methimazole)	Delayed effect seen due to preformed thyroid hormone release; thyroid storm dose higher (load 600–1000 mg, then 200–250 mg every 4 h; PTU preferred over methimazole) Agranulocytosis occurred in 0.2%–0.4% of patients receiving ATDs in 3 studies involving >22 000 patients
I-131	Destroys iodine-avid thyroid tissue	10–30 mCi	Reduction in thyroid hormone values in 2–3 mo	Transient exacerbation of thyrotoxicosis possible; worsening of Graves orbitopathy	Contraindicated in pregnancy; avoid with moderate to severe Graves orbitopathy
Iopanoic acid	Blocks T_4-to-T_3 conversion	500–1000 mg orally once daily	Potent blocker of T_4-to-T_3 conversion	Precludes use of I-131 until iodine cleared	Do not use before ATD; rapid preoperative preparation For thyroid storm, do not start until 1 h after starting ATDs Not available in the United States
Saturated solution of potassium iodide (SSKI, Lugol solution)	Blocks thyroid hormone release	5 drops 4 times daily	Ease of administration	Iodine allergy (true iodine allergy is rare); precludes use of I-131 until iodine cleared	Do not use before ATD; preoperative preparation for thyroidectomy and treatment of thyroid storm
NSAIDs	Anti-inflammatory effects	–	Fewer adverse effects than steroids	Gastrointestinal irritation	Subacute thyroiditis only; can use naproxen, ibuprofen, or other NSAID
Hydrocortisone	Blocks T_4-to-T_3 conversion, anti-inflammatory effects	300 mg intravenous loading followed by 100 mg 3 times daily	Treats coexisting adrenal insufficiency and vasomotor instability	Hyperglycemia	For thyroid storm, 300 mg intravenous loading followed by 100 mg every 8 h
Prednisone	Anti-inflammatory effects	40–60 mg/d	Rapid relief of pain in subacute thyroiditis	Cushing syndrome	Subacute thyroiditis and type 2 amiodarone-induced thyrotoxicosis only

Continued on following page

Table 3–Continued

Agent	*Mechanism of Action*	*Dosage*	*Benefits*	*Adverse Effects*	*Notes*
Lithium	Blocks thyroid hormone release	300 mg 4 times daily	Adjunctive therapy	Neurologic, renal, gastrointestinal, cardiac	Must monitor levels For thyroid storm, adjust dose to maintain therapeutic range; questionable benefit beyond potassium iodide
Cholestyramine	Binds thyroid hormone in the intestines	1–2 g twice daily	Adjunctive therapy	Gastrointestinal	–
Plasmapheresis	Removes T_4/T_3 from circulation	Once or twice	Adjunctive therapy	–	Thyroid storm or before surgery or I-131 if toxicity to ATD

ATD = antithyroid drug; I-131 = radioactive iodine; NSAID = nonsteroidal anti-inflammatory drug; PTU = propylthiouracil; ULN = upper limit of normal.

asymptomatic, the serum TSH level is normal, and TRAb levels are negative (1, 18). Remission occurs in approximately 50% of patients; however, longer treatment periods of up to 5 years may significantly improve the remission rate (19). In patients who were initially TRAb-positive, a negative TRAb level at the end of treatment strongly predicts remission, whereas a persistently positive TRAb level predicts relapse once methimazole therapy is discontinued (1, 20, 21). Similarly, persistently suppressed serum TSH levels with use of methimazole predict relapse if use of the drug is stopped (1, 20, 21). When methimazole therapy cannot be stopped because of persistently positive TRAb levels or suppressed TSH or if Graves disease recurs after discontinuation of therapy, radioactive iodine (I-131) ablation or thyroidectomy is usually recommended. Alternatively, methimazole can be given at low doses (≤10 mg/d) as long-term therapy in patients who prefer this (1, 22, 23).

ATDs effectively reduce thyroid hormone levels in patients with toxic multinodular goiters or toxic thyroid adenomas, but they do not promote remission in these conditions (hyperthyroidism recurs after ATD therapy discontinuation). Therefore, I-131 therapy or thyroidectomy is the preferred primary treatment for these disorders. Nonetheless, long-term low-dose methimazole is reasonable for patients who choose this option (1). Before I-131 or thyroidectomy, methimazole is often prescribed to control hyperthyroidism and reduce risk for posttreatment thyroid storm (1). Methimazole therapy should be stopped 7 days before I-131 administration or just before thyroidectomy (1).

ATDs are not effective in low-RAIU thyrotoxicosis and should not be used in these conditions. Furthermore, low-RAIU thyrotoxic disorders tend to be self-limiting and, depending on the cause, usually respond symptomatically to β-blockers, nonsteroidal anti-inflammatory drugs, or glucocorticoid therapy (1). One exception is type 1 AIT, which may respond to an ATD (1, 14).

Minor adverse effects of ATDs include rashes and liver enzyme elevations (cholestatic markers [alkaline phosphatase and bilirubin] with methimazole and hepatocellular enzymes [aspartate aminotransferase and alanine aminotransferase] with PTU) (1, 16–18, 24). Of note, mild to moderate liver enzyme elevations may be present at baseline due to thyrotoxicosis itself and often resolve after initiation of ATD therapy (1); however, it is recommended that ATD therapy should not be started when hepatic en-

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zyme levels exceed 3 times the ULN and should be discontinued if hepatic enzyme levels increase to these levels during treatment (1). Because PTU can cause severe hepatocellular necrosis with liver failure (25, 26), in 2009 the U.S. Food and Drug Administration advised clinicians to use methimazole instead of PTU except in cases of methimazole allergy and in pregnant women during the first trimester (1, 16–18). Agranulocytosis, a potentially life-threatening disorder, develops in 0.2%–0.4% of patients taking either ATD (1, 27), most often within the first few months; it occurs more commonly with high doses (≥40 mg/d) of methimazole but is not related to PTU dose (1). Agranulocytosis often resolves after discontinuation of therapy but may persist and require bone marrow–specific therapies if it is not recognized and use of the medication is not promptly stopped. PTU may also occasionally cause an antineutrophil cytoplasmic antibody–positive vasculitis (28). When given to pregnant women in the first trimester, methimazole has been associated with aplasia cutis, choanal atresia, and other birth defects; similar birth defects have been reported with PTU but are less common (1, 24, 29, 30). Therefore, it is recommended that pregnant women with Graves disease be treated with PTU during the first trimester and then switched to methimazole in the second and third trimesters (1, 30).

Cold (nonradioactive) iodine (oral potassium iodide) has been reported to be effective long-term therapy for patients with Graves disease who do not tolerate an ATD but decline or have contraindications to I-131 or thyroidectomy (31).

Type 1 AIT (iodine-induced) is usually treated with methimazole (with or without perchlorate if available), and type 2 AIT (thyroiditis) is best treated with oral glucocorticoid therapy. Methimazole and glucocorticoids are sometimes used together when the distinction between types 1 and 2 is not definitive (14). Some patients are resistant to even high doses of these medications; thyroidectomy is an effective option in these patients (32).

When should clinicians consider I-131 ablation as primary therapy?

I-131 ablation is another primary therapy option for Graves disease. It has a long record of efficacy and safety (1, 16) and is also a good choice for secondary therapy in patients with Graves disease who do not have remission with primary ATD treatment (1, 16).

Patients with Graves disease should be given an I-131 dose that is sufficient to cause hypothyroidism (1, 16)— usually about 10–15 mCi as a fixed dose or a calculated dose based on gland size and RAIU (1, 16). Approximately 90% of patients with Graves disease respond well and become hypothyroid within 3–6 months of I-131 administration; both free T_4 and TSH should be monitored routinely during that time so that hypothyroidism can be promptly recognized and treated (1, 33). For patients who do not respond to the initial I-131 dose, retreatment can be considered 3–6 months later. Sialadenitis is an occasional adverse effect from I-131 uptake by the salivary glands.

Pregnancy is an absolute contraindication for I-131 ablation (1, 30) because this radioisotope can destroy the developing fetal thyroid gland. Therefore, women of childbearing potential should always have a documented negative pregnancy test result imme-

diately before receiving I-131 (1, 30). Other contraindications to I-131 therapy include lactation, diagnosed or suspected thyroid cancer, and the presence of significant Graves orbitopathy (GO) (1).

Worsening of preexisting GO is a well-recognized complication of I-131 treatment (34, 35). Other risk factors for GO progression include smoking, high serum TRAb levels, and untreated hyperthyroidism (1). Patients with inactive or mild GO but no risk factors for progression can receive I-131 with minimal concern for worsening of GO. However, patients who have mild GO with risk factors or have moderate to severe GO should receive oral glucocorticoid coverage if I-131 is their chosen therapy (1). The recommended prednisone dose is 0.4–0.5 mg/kg of body weight per day for 1 month starting 1–3 days after I-131 administration, with tapering over the ensuing 2 months (1). In addition, smoking cessation should be strongly encouraged in all patients.

I-131 is 1 of the 2 preferred primary therapy options for toxic multinodular goiters and toxic thyroid adenomas (1). Hypothyroidism is the main adverse effect, occurring in 50%–75% of treated patients. The I-131 doses required in these patients are approximately 20–30 mCi. Because GO does not occur in these conditions, glucocorticoid coverage is not necessary. I-131 therapy is not effective in low-RAIU thyrotoxicosis and should not be used (1).

Serum T_4 and T_3 levels often increase transiently in the first 1–2 weeks after I-131 administration (1). This can exacerbate thyrotoxic symptoms and has been reported to precipitate thyroid storm in persons with severe pretreatment hyperthyroidism (1, 16). Experts recommend treating highly symptomatic patients or those with free T_4 levels that exceed the ULN by more than 2-fold with methimazole, β-blockers, or both for up to a month before I-131 therapy (1, 16). Methimazole therapy should then be discontinued 7 days before I-131 administration because it can reduce the effectiveness of I-131 therapy (1).

When should clinicians consider thyroidectomy as primary therapy?

Thyroidectomy can be considered as primary therapy for any patient with hyperthyroidism (1), in patients with Graves disease who do not achieve remission with primary ATD therapy, in patients who have moderate to severe GO, and in refractory cases of AIT (32). Thyroidectomy is also recommended for hyperthyroid patients who have thyroid nodules that could be cancerous, for patients who decline or cannot tolerate other forms of therapy, and for pregnant women during the second trimester if hyperthyroidism cannot be controlled with an ATD.

Clinicians should prescribe methimazole for at least a month to achieve euthyroidism before surgery (1). Patients with Graves disease, but not those with toxic multinodular goiters or toxic adenomas, should also receive oral potassium iodide during the week before surgery to further reduce thyroid hormone levels and to reduce thyroid vascularity (1). Other options for reducing thyroid hormone levels in patients who are unable to tolerate ATDs include lithium, bile acid sequestrants, iopanoic acid, and plasmapheresis.

Outcomes are best when a high-volume thyroid surgeon does the procedure (36). Most patients are rendered hypothyroid by surgery

and should start replacement L-thyroxine doses (1.6 mcg/kg per day) before discharge from the hospital (1). Thyroidectomy is not indicated for low-RAIU thyrotoxicosis other than for patients with refractory AIT (32).

Radiofrequency ablation of solitary or multiple toxic thyroid nodules can be effective when done by experienced operators for patients who prefer to avoid or have contraindications to I-131 therapy or thyroidectomy (1).

How should clinicians monitor patients who are being treated for hyperthyroidism?

After starting ATD treatment, thyroid tests (measurement of TSH, free T_4, and total T_3 [if T_3 was initially elevated]) should be done every month for 3 months (**Appendix Table 2**, available at Annals.org). Once thyrotoxic symptoms have resolved and thyroid test results are within the reference range, β-blocker use can be stopped and the ATD dose can usually be reduced by 30%–50%. Thyroid testing should then be done every 3–6 months. In patients with Graves disease, if the serum TSH level is normal and the serum TRAb level becomes negative after 12–18 months, ATD therapy can be tapered or stopped to determine whether remission has occurred (1, 16). A normal serum TSH level during treatment and a negative TRAb level at 12–18 months predict a high likelihood of remission, whereas a persistently low TSH level and a positive TRAb level indicate that remission has not occurred (1, 16, 20, 21). Because remission does not occur with toxic multinodular goiters and toxic thyroid adenomas, if long-term methimazole therapy is chosen, regular monitoring of TSH with or without free T_4 should be done every 6–12 months, with a goal of maintaining the serum TSH level (and free T_4 level if measured) within the reference range (1).

When an ATD is prescribed, clinicians should consider ordering a baseline complete blood count (CBC) and liver panel because abnormalities of these tests can result from the presence of thyrotoxicosis at baseline or may develop later as an adverse drug effect. Patients should be advised to notify their provider if they develop symptoms of agranulocytosis (fever, sore throat) or symptoms suggestive of liver injury (jaundice, dark urine, pruritus, abdominal pain, nausea, vomiting) or vasculitis (fatigue, arthralgias) (1, 16–18). A CBC, liver panel, and/or erythrocyte sedimentation rate should then be ordered, as appropriate, and use of the ATD should be discontinued if these severe adverse effects are identified (1). However, routine monitoring of the CBC and liver enzyme levels is not recommended in the absence of suspected ATD toxicity.

Patients who receive I-131 should have a repeated clinical assessment and thyroid tests 2–3 months later (1, 16). Of note, serum TSH levels may remain suppressed for up to 6 weeks after chronically elevated T_4 and T_3 levels decrease into or below the normal range (33). Therefore, it is important to measure free T_4 along with TSH levels in the first 2–3 months after I-131 therapy; during this time, hypothyroidism is often characterized by low serum free T_4 levels with persistently low or normal TSH levels (1, 33). Accordingly, thyroid hormone replacement therapy should be started when the free T_4 level becomes low, even if TSH is not elevated; measurement of serum free T_4 and TSH levels should then be repeated 6–8 weeks later (1). Once the pituitary gland recovers from chronic suppression, serum TSH levels again become reliable and are the best test for monitoring replacement therapy. TSH levels should thereafter be maintained within the reference range. After thyroidectomy for hyperthyroidism, a full replacement dose of L-thyroxine (1.6 mcg/kg daily) should be started at or before hospital discharge (1). Serum TSH should be measured 6–8 weeks later and the L-thyroxine dose should be adjusted at 6- to 8-week intervals until the TSH level is within the reference range; it can then be monitored annually.

What are long-term considerations for the primary treatment options for hyperthyroidism?

Increased cardiovascular morbidity and mortality have been reported in patients with treated hyperthyroidism; however, this seems to be due to the overall duration of insufficiently treated hyperthyroidism rather than the treatment method (37–39). Cancer risk has been another area of interest. Two previous studies did not find a significant increase in any type of cancer after I-131 therapy (40, 41). Subsequently, a study of 18 805 patients reported small but statistically significant associations between prior I-131 therapy and mortality from all solid tumors combined, including female breast cancer (42).

What is subclinical thyrotoxicosis, and what are the indications for treatment?

Subclinical thyrotoxicosis is a term used for mild thyrotoxicosis that manifests primarily as low serum TSH levels and serum free T_4 and total T_3 levels that are still within the reference ranges (1, 43, 44). Most patients are asymptomatic, but some have mild

Treatment of Thyroid Storm

Decrease thyroid hormone synthesis

- Propylthiouracil (oral, rectal, nasogastric tube): 600–1200 mg/d (divided doses)
- Methimazole (oral, rectal, nasogastric tube, intravenous): 60–120 mg/d (divided doses)

Inhibit thyroid hormone release

- Sodium iodide (intravenous): 1 g over 24 hours
- Potassium iodide (oral): 5 drops 4 times a day (SSKI)

Reduce the heart rate

- Esmolol (intravenous): 500 mg over 1 minute, then 50–100 mg/kg per minute
- Metoprolol (intravenous): 5–10 mg every 2–4 hours
- Propranolol (oral): 60–80 mg every 4 hours
- Diltiazem (intravenous): 0.25 mg/kg over 2 minutes, then infusion of 10 mg/min
- Diltiazem (oral): 60–90 mg every 6–8 hours

Support the circulation

- Glucocorticoids in stress doses
- Fluids, oxygen, cooling

Perform plasmapheresis (can be used in patients who have experienced previous significant toxicity to antithyroid drugs)

Treat precipitating cause

symptoms consistent with thyrotoxicosis. Care must be taken to ensure that this diagnosis is correct because similar thyroid hormone profiles may be seen in other conditions, such as normal pregnancy, gestational thyrotoxicosis, hyperemesis gravidarum, nonthyroidal illness syndrome, and central hypothyroidism (hypothalamic–pituitary disease), and with use of certain medications, especially glucocorticoids, dopamine, bexarotene, mitotane, metformin, and heparin (2). When subclinical thyrotoxicosis is due to hyperthyroidism (Graves disease, toxic multinodular goiter, toxic thyroid adenoma), TRAb levels are usually positive or borderline positive (Graves disease), the RAIU is typically within the reference range but inappropriately normal for a low TSH level, and thyroid scan findings are consistent with the underlying cause (1).

Treatment may be considered for subclinical hyperthyroidism (Graves disease, toxic multinodular goiter, toxic thyroid adenoma) but is usually not necessary for other types of subclinical thyrotoxicosis (1). Experts disagree about whether subclinical hyperthyroidism requires treatment because many patients have no or only mild symptoms and the long-term course is variable (1, 43, 44); serum TSH levels sometimes return to normal within 6–12 months without treatment. However, older patients with subclinical hyperthyroidism are at increased risk for atrial fibrillation, heart failure, osteoporotic fractures, and early death (45–49). Therefore, current guidelines recommend treating patients with serum TSH levels less than 0.1 mU/L, those who are definitely symptomatic, and those older than 65 years (1, 3, 43). Debate continues about the optimal management of asymptomatic younger patients with TSH levels that are low but at least 0.1 mU/L; in this situation, clinical judgment and shared decision making are paramount (1, 43). Low-dose methimazole, 5–10 mg/d (or lower), is the most common treatment for subclinical hyperthyroidism (1), but I-131 ablation and thyroidectomy are still options.

How is thyroid storm recognized and treated?

Thyroid storm, also called thyrotoxic crisis or decompensated thyrotoxicosis, is a life-threatening emergency characterized by exaggerated manifestations of thyrotoxicosis (50–54). It usually occurs in patients with unrecognized or inadequately treated hyperthyroidism combined with a precipitating event, such as thyroidectomy, nonthyroid surgery, infection, trauma, or recent I-131 therapy. Fever (temperature >102 °F) is a cardinal manifestation. Supraventricular tachycardia, atrial fibrillation, heart failure, and ischemic heart symptoms develop frequently, and nausea, vomiting, diarrhea, and abdominal pain are also common features. Central nervous system manifestations include hyperkinesis, psychosis, and coma. Serum free T_4 and total T_3 levels are often highly elevated, and the TSH level is usually undetectable.

Although serum TSH levels are low and free T_4 and/or total T_3 levels are elevated in this condition, the hormone levels do not reliably distinguish patients with thyroid storm from those with uncomplicated thyrotoxicosis. Therefore, clinical judgment by an experienced clinician is the key to diagnosis. Validated scoring systems are available to help clinicians determine when this diagnosis is likely (50, 51) (**Appendix Table 3**, available at Annals.org), but a scoring tool should not override clinical judgment.

The immediate goals of therapy (50–54) for thyroid storm are 1) decrease thyroid hormone synthesis with an ATD (methimazole or PTU [both can be given orally, by nasogastric tube, or rectally, and methimazole can be given intravenously; PTU is typically used because it also decreases T_4-to-T_3 conversion]); 2) inhibit thyroid hormone secretion with oral potassium iodide or intravenous sodium iodide; 3) reduce the heart rate with a β-blocker (esmolol, metoprolol, propranolol) and/or a calcium-channel blocker; 4) support the circulation with stress doses of intravenous glucocorticoids, intrave-

nous fluids, oxygen, and cooling (for severe hyperthermia); and 5) identify and treat the precipitating condition (see the Box: Treatment of Thyroid Storm). Plasmapheresis can be used to rapidly reduce serum thyroid hormone levels in patients who have previously had significant toxicity with an ATD. When thyroid storm was first described, the acute mortality rate was nearly 100% (50). The prognosis today is significantly better when the condition is promptly diagnosed and aggressive therapy is instituted; mortality rates in recent reports have been less than 10% (52–54).

When should patients be hospitalized?

Thyrotoxic patients should be hospitalized if thyroid storm is confirmed or suspected. Hospitalization should also be considered for patients who develop ATD-related agranulocytosis, severe liver toxicity, or severe vasculitis.

When should clinicians consider consulting an endocrinologist or ophthalmologist?

Clinicians should consider consulting an endocrinologist for help developing an optimal management plan, when unexpected events or treatment complications occur, when significant GO is present, if the patient is pregnant, and when thyroid storm is present or suspected. Clinicians should consider consulting an ophthalmologist when the patient has double vision; impaired visual acuity, visual fields, or color vision; significant eye discomfort; proptosis greater than 22 mm (with an exophthalmometer, if available); or extraocular muscle dysfunction.

Treatment... Thyrotoxicosis with positive TRAb levels or high or normal RAIU (Graves disease, toxic multinodular goiter, toxic thyroid adenoma) usually requires treatment with an ATD, I-131 ablation, or thyroidectomy. Clinicians should inform patients about the benefits and risks of each possible therapy, after which shared decision making is appropriate. Thyrotoxicosis with negative TRAb levels and low RAIU usually resolves within 3 months (except for AIT) and is best treated with β-blockers to control symptoms until the underlying disorder resolves.

CLINICAL BOTTOM LINE

Practice Improvement

What measures do stakeholders use to evaluate the quality of care for patients with thyrotoxicosis?

Federal legislation passed in 2006 required the Centers for Medicare & Medicaid Services (CMS) to create a physician reporting system for quality measures regarding covered services furnished to Medicare beneficiaries. CMS named this program the Physician Quality Reporting Initiative (PQRI). Eligible professionals who meet the criteria for satisfactory submission of data for services can earn incentive payments. The 2012 PQRI consists of 318 quality measures; however, none specifically applies to persons with hyperthyroidism.

What do professional organizations recommend regarding care of patients with thyrotoxicosis?

Professional associations (1, 55, 56) have published evidence-based guidelines for management of thyrotoxicosis. A shared decision-making tool has been developed to assist patients and providers when choosing an individualized treatment plan for Graves disease (57).

In the Clinic
Tool Kit

Hyperthyroidism

Patient Information

https://medlineplus.gov/hyperthyroidism.html
Patient information and handouts on hyperthyroidism from the National Institutes of Health's MedlinePlus.

www.niddk.nih.gov/health-information/endocrine-diseases/hyperthyroidism
Resources for patients on hyperthyroidism from the National Institute of Diabetes and Digestive and Kidney Diseases.

www.thyroid.org/hyperthyroidism

www.thyroid.org/hipertiroidismo
Frequently asked questions on hyperthyroidism in English and Spanish from the American Thyroid Association.

Information for Health Professionals

www.aafp.org/afp/2016/0301/p363.html
Recommendations for diagnosis and treatment of hyperthyroidism from the American Academy of Family Physicians.

https://annals.org/aim/fullarticle/2208599/screening-thyroid-dysfunction-u-s-preventive-services-task-force-recommendation
2015 recommendation statement on screening for thyroid dysfunction from the U.S. Preventive Services Task Force.

www.liebertpub.com/doi/full/10.1089/thy.2016.0229
2016 guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis from the American Thyroid Association.

www.karger.com/article/fulltext/490384
2018 guidelines for the management of Graves hyperthyroidism from the European Thyroid Association.

www.karger.com/Article/Fulltext/486957
2018 guidelines for the management of amiodarone-associated thyroid dysfunction from the European Thyroid Association.

WHAT YOU SHOULD KNOW ABOUT HYPERTHYROIDISM

What Is Hyperthyroidism?

The thyroid gland is a small gland in the front of your neck. It makes hormones that control how the body uses energy. Hyperthyroidism develops when the thyroid gland makes more thyroid hormone than your body needs. There can be several causes, including:

- Graves disease (an autoimmune disorder, and the most common cause)
- Multiple nodules, or lumps, on the thyroid; this is known as toxic nodular goiter
- A single, toxic lump on the thyroid; this is called toxic adenoma
- Thyroiditis, which is an inflammation of the thyroid gland that causes stored hormones to leak into the body

What Are Common Symptoms?

- Weight loss
- Nervousness or anxiety
- Feeling too hot and/or excessive sweating
- Shortness of breath
- Rapid heartbeat
- Trembling hands
- Frequent bowel movements
- Tiredness
- Changes in mood
- Eye irritation or discomfort

Sometimes, people with hyperthyroidism have no symptoms. Elderly persons may have milder symptoms that include tiredness, depression, weight loss, and rapid heartbeat.

Sometimes, people have sudden onset of severe symptoms like high fever, irregular heartbeat, shortness of breath, chest pain, or stomach pain. Patients with severe symptoms should go to the hospital right away.

Am I at Risk?

Hyperthyroidism is more common in women than in men, especially in those older than 50 years. You may also be at higher risk if you have any of the following:

- A goiter (swelling of the thyroid gland in the front of your neck)
- Certain medical conditions, such as type 1 diabetes or other autoimmune disorders
- A family history of thyroid disorder
- Use of certain medications

How Is It Diagnosed?

- Your doctor will ask about your symptoms and medical history and examine you. The physical examination will include feeling your neck, where the thyroid gland is.
- You will have blood tests to measure your thyroid hormone levels.
- Your doctor may order a test that measures the ability of the thyroid gland to collect iodine (an RAIU, or radioactive iodine uptake test) and a thyroid scan to identify what is causing your hyperthyroidism.
- Your doctor may want to obtain an ultrasound of your thyroid and additional blood testing if the cause is unclear or if you are pregnant or breastfeeding.

How Is It Treated?

Treatment depends on the cause and severity of the hyperthyroidism as well as your age, physical condition, and preferences.

- Beta-blockers can help control your symptoms, including rapid heartbeat, tremors, anxiety, and heat intolerance. Symptoms usually get better very soon after these medicines are started.
- Medications called antithyroid drugs may be used to reduce the amount of hormone your thyroid gland makes.
- Radiation to destroy the thyroid, called radioactive iodine ablation, is a permanent treatment.
- The thyroid may be removed surgically.

Talk to your doctor about the benefits and risks of these options and your personal preference.

Until your hyperthyroidism is under control, you should avoid strenuous physical activity; reduce or eliminate caffeine; stop smoking; avoid products containing iodine, like kelp, iodine supplements, and iodinated contrast agents; and avoid biotin supplements.

Questions for My Doctor

- Do I need to take medicine to treat my hyperthyroidism?
- How long will I have to take the medicine?
- Will I need surgery?
- Are there risks or side effects from the treatment?
- How often should I have follow-up visits and blood testing?
- Will I need to see any other doctors?

For More Information

ACP
American College of Physicians
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American Thyroid Association
www.thyroid.org/hyperthyroidism

Medline Plus
https://medlineplus.gov/hyperthyroidism.html

Patient Information

Appendix Table 1. **History and Physical Examination in Overt Thyrotoxicosis***

Symptom or Finding	*Frequency*
History	
Symptoms of general thyrotoxicosis	
Weight loss	61%–85%
Heat intolerance	55%–89%
Tremulousness	54%
Palpitations	51%–89%
Nervousness/anxiety	41%–99%
Emotional lability	30%–60%
Increased stool frequency	22%–33%
Neck fullness	22%
Eye symptoms	11%–54%
Dyspnea	10%–75%
Weight gain	2%–12%
Fatigue	69%–88%
Excessive sweating	45%–91%
Increased appetite	42%–65%
Symptoms specific for Graves disease	
Eye swelling	NR, variable
Eye redness	NR, variable
Eye pain	NR, variable
Rash on shins	NR, variable
Symptoms specific for subacute thyroiditis	
Neck pain	NR, variable
Sore throat	NR, variable
Fever	NR, variable
Physical examination	
Findings of general thyrotoxicosis	
Palpable goiter	69%–100%
Hand tremor	42%–97%
Adrenergic eye signs (stare, lid lag)	34%–71%
Moist skin	34%
Tachycardia	80%–100%
Atrial fibrillation	3%–10%
Findings specific for Graves disease	
Diffuse goiter	NR, variable
Bruit over goiter	NR, variable
Infiltrative orbitopathy (proptosis, periorbital edema)	NR, variable
Pretibial myxedema	NR, variable
Thyroid acropachy	NR, variable
Findings specific for toxic multinodular goiter	
Palpable thyroid nodules	NR, variable
Findings specific for toxic thyroid adenoma	
Palpable thyroid nodule	NR, variable
Findings specific for subacute thyroiditis	
Fever	NR, variable
Thyroid tenderness	NR, variable

NR = not reported.
** Data compiled and adapted from references 7 to 9.*

Appendix Table 2. **Elements of Follow-up for Thyrotoxicosis**

Issue	*Method of Evaluation*	*Frequency*	*Notes*
History			
Response to therapy	Ask patient	Every visit	–
Drug adherence and adverse effects	Ask patient	Every visit	Patients taking antithyroid drugs
Physical examination			
Response to therapy	Weigh patient	Every visit	–
Response to therapy	Determine cardiac rate and rhythm	Every visit	Maintain heart rate <90 beats/min; obtain electrocardiogram if heart rate is irregular to exclude atrial fibrillation Expect decrease in flow murmur with treatment
Response to therapy	Careful thyroid palpation	Every visit	Expect decrease in goiter size with successful Graves disease treatment
Evaluation of eye signs, including those specific to Graves disease	–	Every visit	–
Other signs specific to Graves disease	Inspect extremities for myxedema and thyroid acropachy	Every visit	Patients with Graves disease and orbitopathy may also develop pretibial myxedema and thyroid acropachy
Laboratory testing			
Response to therapy	Obtain free T_4 and second- or third-generation TSH	Every visit until stable on antithyroid drug regimen	T_4 improves more rapidly than TSH Prolonged TSH suppression possible after treatment of moderate to severe thyrotoxicosis
Response to therapy	Measure TSH and TRAb levels	After 12–18 mo of antithyroid drug therapy	To determine whether remission of Graves disease has occurred
Drug adverse effects	Liver function tests, CBC	Immediately if agranulocytosis (fever, sore throat) or liver toxicity suspected; erythrocyte sedimentation rate if vasculitis suspected during propylthiouracil treatment Routine monitoring not recommended	Routine measurement not proven to be cost-effective Methimazole manufacturer recommends performing liver function tests in the event of anorexia, pruritus, jaundice, or right upper quadrant abdominal pain and stopping therapy for aminotransferase elevations >3 times the upper limit of normal
Change in thyroid examination	Ultrasonography	When needed for new nodule or unexpected scan defect (cold)	–
Drug therapy			
Response to therapy; drug adverse effects	Adjust dose or change therapy as needed	As needed	–
Patient education			
Course of disease and management	Discuss expected course and potential adverse effects of treatment	Each visit	–

CBC = complete blood count; TRAb = thyrotropin receptor antibody; TSH = thyroid-stimulating hormone.

Appendix Table 3. **Thyroid Storm Scoring System***

Feature	*Score*
Fever	
99–99.9 °F	5
100–100.9 °F	10
101–101.9 °F	15
102–102.9 °F	20
103–103.9 °F	25
≥104 °F	30
Central nervous system symptoms	
Absent	0
Mild agitation	10
Moderate	20
Severe	30
Cardiac findings	
Pulse	
99–109 beats/min	5
110–119 beats/min	10
120–129 beats/min	15
130–139 beats/min	20
≥140 beats/min	25
Atrial fibrillation	10
Congestive heart failure	
Absent	0
Mild (edema)	5
Moderate (rales)	10
Severe (pulmonary edema)	15
Gastrointestinal symptoms	
Absent	0
Nausea, vomiting, diarrhea, pain	10
Jaundice	20
Precipitant history	
Absent	0
Present	10
Score	
<25	Thyroid storm unlikely
25–44	Suggestive of thyroid storm
≥45	Thyroid storm likely

* *From reference 50.*