HYPERTHYROIDISM AND OTHER CAUSES OF THYROTOXICOSIS: MANAGEMENT GUIDELINES OF THE AMERICAN THYROID ASSOCIATION AND AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

Rebecca S. Bahn (Chair), MD[1,]; Henry B. Burch, MD[2]; David S. Cooper, MD[3]; Jeffrey R. Garber, MD, FACP, FACE[4]; M. Carol Greenlee, MD [5]; Irwin Klein, MD[6]; Peter Laurberg, MD[7]; I. Ross McDougall, MD[8]; Victor M. Montori, MD[1]; Scott A. Rivkees, MD[9]; Douglas S. Ross, MD[10]; Julie Ann Sosa, MD[11]; Marius N. Stan, MD[1]*

American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health-care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

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ABSTRACT

Objective: Thyrotoxicosis has multiple etiologies, manifestations, and potential therapies. Appropriate treatment requires an accurate diagnosis and is influenced by coexisting medical conditions and patient preference. This article describes evidence-based clinical guidelines for the management of thyrotoxicosis that would be useful to generalist and subspeciality physicians and others providing care for patients with this condition.

Methods: The development of these guidelines was commissioned by the American Thyroid Association in association with the American Association of Clinical Endocrinologists. The American Thyroid Association and American Association of Clinical Endocrinologists assembled a task force of expert clinicians who authored this report. The task force examined relevant literature using a systematic PubMed search supplemented with additional published materials. An evidence-based medicine approach that incorporated the knowledge and experience of the panel was used to develop the text and a series of specific recommendations. The strength of the recommendations and the quality of evidence supporting each was rated according to the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation Group.

Results: Clinical topics addressed include the initial evaluation and management of thyrotoxicosis; management of Graves' hyperthyroidism using radioactive iodine, antithyroid drugs, or surgery; management of toxic multinodular goiter or toxic adenoma using radioactive iodine or surgery; Graves' disease in children, adolescents, or pregnant patients; subclinical hyperthyroidism; hyperthyroidism in patients with Graves' ophthalmopathy; and management of other miscellaneous causes of thyrotoxicosis.

Conclusions: One hundred evidence-based recommendations were developed to aid in the care of patients with thyrotoxicosis and to share what the task force believes is current, rational, and optimal medical practice.

For accompanying editorial, see page 325

INTRODUCTION

Thyrotoxicosis is a condition having multiple etiologies, manifestations, and potential therapies. The term "thyrotoxicosis" refers to a clinical state that results from inappropriately high thyroid hormone action in tissues generally due to inappropriately high tissue thyroid hormone levels. The term "hyperthyroidism," as used in these guidelines, is a form of thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormone(s) by the thyroid. Appropriate treatment of thyrotoxicosis requires

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By mutual agreement among the authors and editors of their respective journals, this work is being published jointly in *Thyroid* and *Endocrine Practice*.

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an accurate diagnosis. For example, thyroidectomy is an appropriate treatment for some forms of thyrotoxicosis and not for others. Additionally, beta blockers may be used in almost all forms of thyrotoxicosis, whereas antithyroid drugs are useful in only some.

In the United States, the prevalence of hyperthyroidism is approximately 1.2% (0.5% overt and 0.7% subclinical); the most common causes include Graves' disease (GD), toxic multinodular goiter (TMNG), and toxic adenoma (TA) (1). Scientific advances relevant to this topic are reported in a wide range of literature, including subspeciality publications in endocrinology, pediatrics, nuclear medicine, and surgery, making it challenging for clinicians to keep abreast of new developments. Although guidelines for the diagnosis and management of patients with hyperthyroidism have been published previously by both the American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE), in conjunction with guidelines for the treatment of hypothyroidism (1,2), both associations determined that thyrotoxicosis represents a priority area in need of updated evidence-based practice guidelines.

The target audience for these guidelines includes general and subspeciality physicians and others providing care for patients with thyrotoxicosis. In this document, we outline what we believe is current, rational, and optimal medical practice. It is not the intent of these guidelines to replace clinical judgment, individual decision making, or the wishes of the patient or family. Rather, each recommendation should be evaluated in light of these elements in order that optimal patient care is delivered. In some circumstances, it may be apparent that the level of care required may be best provided in centers where there is specific expertise, and that referral to such centers should be considered.

METHODS OF DEVELOPMENT OF EVIDENCE-BASED GUIDELINES

Administration

The ATA Executive Council and the Executive Committee of AACE forged an agreement outlining the working relationship between the two groups surrounding the development and dissemination of management guidelines for the treatment of patients with thyrotoxicosis. A chairperson was selected to lead the task force and this individual (R.S.B.) identified the other 11 members of the panel in consultation with the ATA and the AACE boards of directors. Membership on the panel was based on clinical expertise, scholarly approach, and representation of adult and pediatric endocrinology, nuclear medicine, and surgery. The task force included individuals from both North America and Europe. In addition, the group recruited an expert on the development of evidence-based guidelines (V.M.M.) to serve in an advisory capacity. Panel members declared whether they had any potential conflict of interest at the initial meeting of the group and periodically during the course of deliberations. Funding for the guidelines was derived solely from the general funds of the ATA and thus the task force functioned without commercial support.

To develop a scholarly and useful document, the task force first developed a list of the most common causes of thyrotoxicosis and the most important questions that a practitioner might pose when caring for a patient with a particular form of thyrotoxicosis or special clinical condition. Two task force members were assigned to review the literature relevant to each of the topics, using a systematic PubMed search for primary references and reviews supplemented with additional published materials available before June 2010, and develop recommendations based on the literature and expert opinion where appropriate. A preliminary document and a series of recommendations concerning all of the topics were generated by each subgroup and then critically reviewed by the task force at large. The panel agreed recommendations would be based on consensus of the panel and that voting would be used if agreement could not be reached. Two recommendations were not unanimous and the dissenting position is noted. Task force deliberations took place during several lengthy committee meetings, multiple telephone conference calls, and through electronic communication.

Rating of the recommendations

These guidelines were developed to combine the best scientific evidence with the experience of seasoned clinicians and the pragmatic realities inherent in implementation. The task force elected to rate the recommendations according to the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Group (3), with a modification in the grading of evidence (4). Although the rating system we chose differs from those used in previous ATA and AACE clinical practice guidelines, the approach conforms with the recently updated AACE protocol for standardized production of clinical practice guidelines (5). The balance between benefits and risks, quality of evidence, applicability, and certainty of the baseline risk are all considered in judgments about the strength of recommendations (6). Grading the quality of the evidence takes into account study design, study quality, consistency of results, and directness of the evidence. The strength of a recommendation is indicated by the number 1 or 2. Grade 1 indicates a strong recommendation (for or against) that applies to most patients in most circumstances with benefits of action clearly outweighing the risks and burdens (or vice versa). In contrast, Grade 2 indicates a weak recommendation or a suggestion that may not be appropriate for every patient, depending on context, patient values, and preferences. The risks and benefits

or burdens associated with a weak recommendation are closely balanced or uncertain and the statement is generally associated with the phrase "we suggest" or "should be considered." The quality of the evidence is indicated by plus signs, such that + denotes low quality evidence; ++, moderate quality evidence; and +++, high quality evidence, based on consistency of results between studies and study design, limitations, and the directness of the evidence. Table 1 describes the criteria to be met for each rating category. Each recommendation is preceded by a description of the evidence and, in some cases, followed by a remarks section including technical suggestions on issues such as dosing and monitoring.

Presentation and endorsement of recommendations

The organization of the task force's recommendations is presented in Table 2. The page numbers and the location key can be used to locate specific topics and recommendations**.** Specific recommendations are presented within boxes in the main body of the text. Location keys can be copied into the Find or Search function in a file or Web page to rapidly navigate to a particular section. A listing of the recommendations without text is provided as Appendix A.

The final document was approved by the ATA and AACE on March 15, 2011, and officially endorsed (in alphabetical order) by American Academy of Otolaryngology–Head and Neck Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, Canadian Paediatric Endocrine Group–Groupe Canadien d'Endocrinologie Pédiatrique (endorsement of pediatric section only), European Association of Nuclear Medicine, The Endocrine Society, European Society of Endocrinology, European Society of Endocrine Surgeons, European Thyroid Association, International Association of Endocrine Surgeons, Latin American Thyroid Society, Pediatric Endocrine Society, Italian Endocrine Society, and Society of Nuclear Medicine.

RESULTS

[A] Background

In general, thyrotoxicosis can occur if (i) the thyroid is inappropriately stimulated by trophic factors; (ii) there is constituitive activation of thyroid hormone synthesis and secretion leading to autonomous release of excess thyroid hormone; (iii) thyroid stores of preformed hormone are passively released in excessive amounts owing to autoimmune, infectious, chemical, or mechanical insult; or (iv) there is exposure to extra-thyroidal sources of thyroid hormone, which may be either endogenous (struma ovarii, metastatic differentiated thyroid cancer) or exogenous (factitious thyrotoxicosis).

Subclinical hyperthyroidism (SH) is most often caused by release of excess thyroid hormone by the gland. This condition is defined as a low or undetectable serum thyroid-stimulating hormone (TSH) with values within the normal reference range for both triiodothyronine (T_3) and free thyroxine (T_4) estimates. Both overt and subclinical disease may lead to characteristic signs and symptoms.

GD is an autoimmune disorder in which thyrotropin receptor antibodies (TRAbs) stimulate the TSH receptor, increasing thyroid hormone production. The natural history of nodular thyroid disease includes growth of established nodules, new nodule formation, and development of autonomy over time (7). In TAs, autonomous hormone production can be caused by somatic activating mutations of genes regulating thyroid hormone systhesis. Germline mutations in the gene encoding the TSH receptor can cause sporadic or familial nonautoimmune hyperthyroidism

Table 1. Grading of Recommendations, Assessment, Development, and Evaluation System

Type of grading	*Definition of grades*
Strength of the recommendation	1 = strong recommendation (for or against) Applies to most patients in most circumstances Benefits clearly outweigh the risk (or vice versa)
	2 = weak recommendation (for or against) Best action may differ depending on circumstances or patient values Benefits and risks or burdens are closely balanced, or uncertain
Quality of the evidence	+++ = High quality; evidence at low risk of bias, such as high quality randomized trials showing consistent results directly applicable to the recommendation
	++ = Moderate quality; studies with methodological flaws, showing inconsistent or indirect evidence
	+ = Low quality; case series or unsystematic clinical observations

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Table 2. Organization of the Task Force's Recommendations

Location key	*Description*	*Page*
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[K]	If surgery is chosen as treatment for TMNG or TA, how should it be accomplished?	477
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[K2]	The surgical procedure and choice of surgeon	478
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[L]	Is there a role for antithyroid drug therapy in patients with TMNG or TA?	479
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[O3]	Monitoring of children taking methimazole	481
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(continued)

Table 2. (Continued)

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GD, Graves' disease; GO, Graves' ophthalmopathy; SH, subclinical hyperthyroidism; TA, toxic adenoma; TMNG, toxic multinodular goiter; TRAb, thyrotropin receptor antibody; TSH, thyroid-stimulating hormone.

associated with a diffuse enlargement of the thyroid gland (8). Autonomous hormone production is caused by somatic, activating mutations of genes regulating follicular cell activities. Hormone production may progress from subclinical to overt hyperthyroidism, and the administration of pharmacologic amounts of iodine to such patients may result in iodine-induced hyperthyroidism (9). GD is overall the most common cause of hyperthyroidism in the United States (10,11). Although toxic nodular goiter is less common than GD, its prevalence increases with age and in the presence of iodine deficiency. Therefore, toxic nodular goiter may actually be more common than GD in older

patients from regions of iodine deficiency (12). Unlike toxic nodular goiter, which is progressive (unless triggered by excessive iodine intake), remission of GD has been reported in up to 30% of patients without treatment (13).

The mechanism of hyperthyroidism in painless and subacute thyroiditis is inflammation of thyroid tissue with release of preformed hormone into the circulation. Painless thyroiditis is the etiology of hyperthyroidism in about 10% of patients (14), occurring in the postpartum period (postpartum thyroiditis) (15), during lithium (16), or cytokine (e.g., interferon-alpha) (17) therapy, and in 5–10% of amiodarone-treated patients (18). Subacute thyroiditis is thought to be caused by viral infection and is characterized by fever and thyroid pain (19).

Thyroid hormone influences almost every tissue and organ system in the body. It increases tissue thermogenesis and basal metabolic rate (BMR) and reduces serum cholesterol levels and systemic vascular resistance. Some of the most profound effects of increased thyroid hormone levels are on the cardiovascular system (20). The complications of untreated thyrotoxicosis include loss of weight, osteoporosis, atrial fibrillation, embolic events, and even cardiovascular collapse and death (21,22).

The cellular actions of thyroid hormone are mediated by T_3, the active form of thyroid hormone. T_3 binds to nuclear receptor proteins that function as transcription factors to regulate the expression of many genes. Nongenomic actions of thyroid hormone also regulate important physiologic parameters.

The signs and symptoms of overt and mild, or subclinical, thyrotoxicosis are similar, but differ in magnitude. Overt thyrotoxicosis, whether endogenous or exogenous, is characterized by excess thyroid hormones in serum and suppressed TSH (<0.01 mU/L). There are also measurable changes in basal metabolic rate, cardiovascular hemodynamics, and psychiatric and neuropsychological function (23). There is only moderate correlation between the elevation in thyroid hormone concentration and clinical signs and symptoms. Symptoms and signs that result from increased adrenergic stimulation include tachycardia and anxiety and appear to be more pronounced in younger patients and those with larger goiters (24).

[B] How should clinically or incidentally discovered thyrotoxicosis be evaluated and initially managed?

[B1] Assessment of disease severity

The assessment of thyrotoxic manifestations, and especially potential cardiovascular and neuromuscular complications, is essential to formulating an appropriate treatment plan. While it might be anticipated that the severity of thyrotoxic symptoms is proportional to the elevation in the serum levels of free T_4 and T_3 estimates, in one study of 25 patients with GD, the Hyperthyroid Symptom Scale did not strongly correlate with free T_4 or T_3 estimates and was inversely correlated with age (24). The importance of age as a determinant of the prevalence and severity of hyperthyroid symptoms has been recently confirmed (25). Cardiac evaluation may be necessary, especially in the older patient, and may require an echocardiogram, electrocardiogram, Holter monitor, or myocardial perfusion studies. In addition to the administration of beta-blockers (26), specific cardiovascular treatment may be directed toward concomitant myocardial ischemia, congestive heart failure, or atrial arrhythmias (20), and anticoagulation may be necessary in patients in atrial fibrillation (27). Goiter size, obstructive symptoms, and the severity of Graves' ophthalmopathy (GO; the inflammatory disease that develops in the orbit in association with autoimmune thyroid disorders can be discordant with the degree of hyperthyroidism or hyperthyroid symptoms.

All patients with known or suspected hyperthyroidism should undergo a comprehensive history and physical examination, including measurement of pulse rate, blood pressure, respiratory rate, and body weight. In addition, thyroid size; presence or absence of thyroid tenderness, symmetry, and nodularity; pulmonary, cardiac, and neuromuscular function (23,26,28); and presence or absence of peripheral edema, eye signs, or pretibial myxedema should be assessed.

[B2] Biochemical evaluation

Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected hyperthyroidism and should be used as an initial screening test (29). However, when hyperthyroidism is strongly suspected, diagnostic accuracy improves when both a serum TSH and free T_4 are assessed at the time of the initial evaluation. The relationship between free T_4 and TSH (when the pituitary-thyroid axis is intact) is an inverse log-linear relationship; therefore, small changes in free T_4 result in large changes in serum TSH concentrations. Serum TSH levels are considerably more sensitive than direct thyroid hormone measurements for assessing thyroid hormone excess (30). In overt hyperthyroidism, usually both serum free T_4 and T_3 estimates are elevated, and serum TSH is undetectable; however, in milder hyperthyroidism, serum T_4 and free T_4 estimates can be normal, only serum T_3 may be elevated, and serum TSH will be <0.01 mU/L (or undectable). These laboratory findings have been called "T_3-toxicosis" and may represent the earliest stages of disease or that caused by an autonomously functioning thyroid nodule. As is the case with T_4, total T_3 measurements are impacted by protein binding. Assays for estimating free T_3 are less widely validated than those for free T_4, and therefore measurement of total T_3 is frequently preferred in clinical practice. Subclincial hyperthyroidism is defined as a normal serum-free T_4 estimate and normal

total T_3 or free T_3 estimate, with subnormal serum TSH concentration. Laboratory protocols that automatically add free T_4 estimate and T_3 measurements when screening serum TSH concentrations are low avoid the need for subsequent blood draws.

In the absence of a TSH-producing pituitary adenoma or thyroid hormone resistance, if the serum TSH is normal, the patient is almost never hyperthyroid. The term "euthyroid hyperthyroxinemia" has been used to describe a number of entities, mostly thyroid hormone-binding protein disorders, that cause elevated *total* serum T_4 concentrations (and frequently elevated *total* serum T_3 concentrations) in the absence of hyperthyroidism (31). These conditions include elevations in T_4 binding globulin (TBG) or transthyretin (TTR) (32), the presence of an abnormal albumin which binds T_4 with high capacity (familial hyperthyroxinemic dysalbuminia), a similarly abnormal TTR, and, rarely, immunoglobulins which directly bind T_4 or T_3. TBG excess may occur as a hereditary X-linked trait, or be acquired as a result of pregnancy or estrogen administration, hepatitis, acute intermittent porphyuria, or during treatment with 5-flourouracil, perphenazine, or some narcotics. Other causes of euthyroid hyperthyroxinemia include those drugs that inhibit T_4 to T_3 conversion, such as amiodarone (18) or high-dose propranolol (26), acute psychosis, extreme high altitude, and amphetamine abuse. Estimates of free thyroid hormone concentrations frequently also give erroneous results in these disorders. Spurious free T_4 elevations may occur in the setting of heparin therapy. When free thyroid hormone concentrations are elevated and TSH is normal or elevated, further evaluation is necessary.

After excluding euthyroid hyperthyroxinemia, TSH-mediated hyperthyroidism should be considered. A pituitary lesion on MRI and a disproportionately high serum level of the alpha-subunit of the pituitary glycoprotein hormones support the diagnosis of a TSH-producing pituitary adenoma (33). A family history and positive result of genetic testing for mutations in the T_3-receptor support a diagnosis of thyroid hormone resistance (34). Rare problems with TSH assays caused by heterophilic antibodies can cause spuriously high TSH values.

[B3] Determination of etiology

■ **RECOMMENDATION 1**

A radioactive iodine uptake should be performed when the clinical presentation of thyrotoxicosis is not diagnostic of GD; a thyroid scan should be added in the presence of thyroid nodularity. **1/+00**

In a patient with a symmetrically enlarged thyroid, recent onset of ophthalmopathy, and moderate to severe hyperthyroidism, the diagnosis of GD is sufficiently likely that further evaluation of hyperthyroidism causation is unnecessary. A radioactive iodine uptake (RAIU) is indicated when the diagnosis is in question (except during pregnancy) and distinguishes causes of thyrotoxicosis having elevated or normal uptake over the thyroid gland from those with near-absent uptake (Table 3). It is usually elevated in patients with GD and normal or high in toxic nodular goiter, unless there has been a recent exposure to iodine (e.g., radiocontrast). The pattern of RAIU in GD is diffuse unless there are coexistent nodules or fibrosis. The pattern of uptake in a patient with a single TA generally shows focal uptake in the adenoma with suppressed uptake in the surrounding and contralateral thyroid tissue.

Table 3. Causes of Thyrotoxicosis

Thyrotoxicosis associated with a normal or elevated radioiodine uptake over the neck[a]
GD
TA or TMNG
Trophoblastic disease
TSH-producing pituitary adenomas
Resistance to thyroid hormone (T_3 receptor mutation)[b]
Thyrotoxicosis associated with a near-absent radioiodine uptake over the neck
Painless (silent) thyroiditis
Amiodarone-induced thyroiditis
Subacute (granulomatous, de Quervain's) thyroiditis
Iatrogenic thyrotoxicosis
Factitious ingestion of thyroid hormone
Struma ovarii
Acute thyroiditis
Extensive metastases from follicular thyroid cancer

[a]In iodine-induced or iodine exposed hyperthyroidism (including amiodarone type 1), the uptake may be low.
[b]Patients are not uniformly clinically hyperthyroid.
T_3, triiodothyronine.

The image in TMNG demonstrates multiple areas of focal increased and suppressed uptake, and if autonomy is extensive, the image may be difficult to distinguish from that of GD (35).

The RAIU will be near zero in patients with painless, postpartum, or subacute thyroiditis, or in those with factitious ingestion of thyroid hormone or recent excess iodine intake. The radioiodine uptake may be low after exposure to iodinated contrast in the preceeding 1–2 months or with ingestion of a diet unusually rich in iodine such as seaweed soup or kelp. However, it is rarely zero unless the iodine exposure is reoccurring as during treatment with amiodarone. When exposure to excess iodine is suspected (e.g., when the RAIU is lower than expected), but not well established from the history, assessment of urinary iodine concentration may be helpful.

Technetium scintigraphy (TcO_4) utilizes pertechnetate that is trapped by the thyroid, but not organified. While this results in a low range of normal uptake and high background activity, total body radiation exposure is less than for ^{123}I scintiscans; either type of scan can be useful in determining the etiology of hyperthyroidism in the presence of thyroid nodularity. Ultrasonography does not generally contribute to the differential diagnosis of thyrotoxicosis. When radioactive iodine is contraindicated, such as during pregnancy or breastfeeding, or not useful, such as following recent iodine exposure, ultrasound showing increased color Doppler flow may be helpful in confirming a diagnosis of thyroid hyperactivity (36). Doppler flow has also been used to distinguish between subtypes of amiodarone-induced thyrotoxicosis (see Section [U3], and between GD and destructive thyroiditis (see Section [V1]). An alternative way to diagnose GD is by measurement of TRAb. This approach is utilized when a thyroid scan and uptake are unavailable or contraindicated (e.g., during pregnancy and nursing). The ratio of total T_3 to total T_4 can also be useful in assessing the etiology of thyrotoxicosis when scintigraphy is contraindicated. Since relatively more T_3 is synthesized than T_4 in a hyperactive gland, the ratio (ng/mcg) is usually >20 in GD and toxic nodular goiter, and <20 in painless or postpartum thyroiditis (37).

In most patients, the distinction between subacute and painless thyroiditis is not difficult. Subacute thyroiditis is generally painful, the gland is firm to hard on palpation, and the erythrocyte sedimentation rate (ESR) is almost always >50 and sometimes over 100 mm/h. Patients with painless thyroiditis may present in the postpartum period, often have a personal or family history of autoimmune thyroid disease, and typically have low to moderate concentrations of antithyroid peroxidase antibodies (38).

Thyroglobulin is released along with thyroid hormone in subacute, painless, and palpation thyroiditis, whereas its release is suppressed in the setting of exogenous thyroid hormone administration. Therefore, if not elucidated by the history, factitious ingestion of thyroid hormone can be distinguished from other causes of thyrotoxicosis by a low serum thyroglobulin level and a near-zero RAIU (39). In patients with antithyroglobulin antibodies, which interfere with thyroglobulin measurement, an alternative but not widely available approach is measurement of fecal T_4 (40).

Technical remarks: Most TRAb assays are specific for GD, but thyroid-stimulating immunoglobulins (TSI) and first-generation thyrotropin-binding inhibitor immunoglobulin (TBII) assays are less sensitive (41,42). For example, one study found a second-generation TBII assay, which utilizes human recombinant TSH receptors, to have a specificity of 99% and a sensitivity of 95% compared to a sensitivity of 68% for a first-generation assay (43).

[B4] Symptomatic management

■ **RECOMMENDATION 2**

Beta-adrenergic blockade should be given to elderly patients with symptomatic thyrotoxicosis and to other thyrotoxic patients with resting heart rates in excess of 90 bpm or coexistent cardiovascular disease. **1/++0**

■ **RECOMMENDATION 3**

Beta-adrenergic blockade should be considered in all patients with symptomatic thyrotoxicosis. **1/+00**

In patients in whom the diagnosis of thyrotoxicosis is strongly suspected or confirmed, treatment with propranolol, atenolol, metoprolol, or other beta-blockers leads to a decrease in heart rate, systolic blood pressure, muscle weakness, and tremor, as well as improvement in the degree of irritability, emotional lability, and exercise intolerance (24).

Technical remarks: Since there is not sufficient beta-1 selectivity of the available beta-blockers at the recommended doses, these drugs are generally contraindicated in patients with bronchospastic asthma. However, in patients with quiescent bronchospastic asthma in whom heart rate control is essential, or in patients with mild obstructive airway disease or symptomatic Raynaud's phenomenon, a nonselective beta-blocker such as nadolol can be used cautiously, with careful monitoring of pulmonary status. Occasionally, very high doses of beta-blockers are required to manage symptoms of thyrotoxicosis and to reduce the heart rate to near the upper limit of normal (Table 4) (26). Calcium channel blockers, both verapamil and diltiazem, when administered orally and not intravenously, have been shown to effect rate control in patients who do not tolerate or are not candidates for beta-adrenergic blocking agents.

Table 4. Beta-Adrenergic Receptor Blockade in the Treatment of Thyrotoxicosis[a]

Drug	*Dosage*	*Frequency*	*Considerations*
Propanolol[b]	10–40 mg	TID-QID	Nonselective beta-adrenergic receptor blockade Longest experience May block T_4 to T_3 conversion at high doses Preferred agent for nursing mothers
Atenolol	25–100 mg	QD or BID	Relative beta -1 selectivity Increased compliance
Metoprolol[b]	25–50 mg	QID	Relative beta -1 selectivity
Nadolol	40–160 mg	QD	Nonselective beta-adrenergic receptor blockade Once daily Least experience to date May block T_4 to T_3 conversion at high doses
Esmolol	IV pump 50– 100 μg/kg/min		In intensive care unit setting of severe thyrotoxicosis or storm

[a]Each of these drugs has been approved for treatment of cardiovascular diseases, but to date none has been approved for the treatment of thyrotoxicosis.
[b]Also available in once daily preparations.
T_4, thyroxine.

[C] How should overt hyperthyroidism due to GD be managed?

■ **RECOMMENDATION 4**
Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: ^{131}I therapy, antithyroid medication, or thyroidectomy. **1/++0**

Once it has been established that the patient is hyperthyroid and the cause is GD, the patient and physician must choose between three effective and relatively safe initial treatment options: ^{131}I therapy (radioactive iodine), antithyroid drugs (ATD), or thyroidectomy (44). In the United States, radioactive iodine has been the therapy most preferred by physicians. In Europe and Japan, there has been a greater physician preference for ATDs and/or surgery (45). The long-term quality of life (QoL) following treatment for GD was found to be the same in patients randomly allocated to one of the three treatment options (46).

Technical remarks: Once the diagnosis has been made, the treating physician and patient should discuss each of the treatment options, including the logistics, benefits, expected speed of recovery, drawbacks, potential side effects, and cost. This sets the stage for the physician to make recommendations based on best clinical judgment and allows the final decision to incorporate the personal values and preferences of the patient.

Factors that favor a particular modality as treatment for Graves' hyperthyroidism:

a. ^{131}I: Females planning a pregnancy in the future (in more than 4–6 months following radioiodine therapy, provided thyroid hormone levels are normal), individuals with comorbidities increasing surgical risk, and patients with previously operated or externally irradiated necks, or lack of access to a high-volume thyroid surgeon or contraindications to ATD use.
b. ATDs: Patients with high likelihood of remission (patients, especially females, with mild disease, small goiters, and negative or low-titer TRAb); the elderly or others with comorbidities increasing surgical risk or with limited life expectancy; individuals in nursing homes or other care facilities who may have limited longevity and are unable to follow radiation safety regulations; patients with previously operated or irradiated necks; patients with lack of access to a high-volume thyroid surgeon; and patients with moderate to severe active GO.
c. Surgery: Symptomatic compression or large goiters (≥80 g); relatively low uptake of radioactive iodine; when thyroid malignancy is documented or suspected (e.g., suspicious or indeterminate cytology); large nonfunctioning, photopenic, or

hypofunctioning nodule; coexisting hyperparathyroidism requiring surgery; females planning a pregnancy in <4–6 months (i.e., before thyroid hormone levels would be normal if radioactive iodine were chosen as therapy), especially if TRAb levels are particularly high; and patients with moderate to severe active GO.

Contraindications to a particular modality as treatment for Graves' hyperthyroidism:

a. ^{131}I therapy: Definite contraindications include pregnancy, lactation, coexisting thyroid cancer, or suspicion of thyroid cancer, individuals unable to comply with radiation safety guidelines and females planning a pregnancy within 4–6 months.
b. ATDs: Definite contraindications to long-term ATD therapy include previous known major adverse reactions to ATDs.
c. Surgery: Factors that may mitigate against the choice of surgery include substantial comorbidity such as cardiopulmonary disease, end-stage cancer, or other debilitating disorders. Pregnancy is a relative contraindication and should only be used in this circumstance, when rapid control of hyperthyroidism is required and antithyroid medications cannot be used. Thyroidectomy is best avoided in the first and third trimesters of pregnancy because of teratogenic effects associated with anesthetic agents and increased risk of fetal loss in the first trimester and increased risk of preterm labor in the third. Optimally, thyroidectomy is performed in the latter portion of the second trimester. Although it is the safest time, it is not without risk (4.5%–5.5% risk of preterm labor) (47,48).

Factors that may impact patient preference:

a. ^{131}I therapy: Patients choosing ^{131}I therapy as treatment for GD would likely place relatively higher value on definitive control of hyperthyroidism, the avoidance of surgery, and the potential side effects of antithyroid medications, as well as a relatively lower value on the need for lifelong thyroid hormone replacement, rapid resolution of hyperthyroidism, and potential worsening or development of GO (49).
b. ATDs: Patients choosing antithyroid drug therapy as treatment for GD would place relatively higher value on the possibility of remission and the avoidance of lifelong thyroid hormone treatment, the avoidance of surgery, and exposure to radioactivity and a relatively lower value on the avoidance of ATD side effects (see section E), the need for continued monitoring and the possibility of disease recurrence.
c. Surgery: Patients choosing surgery as treatment for GD would likely place a relatively higher value on prompt and definitive control of hyperthyroidism, avoidance of exposure to radioactivity, and the potential side effects of ATDs and a relatively lower value on potential surgical risks and need for lifelong thyroid hormone replacement.

[D] If ^{131}I therapy is chosen, how should it be accomplished?

[D1] Preparation of patients with GD for ^{131}I therapy

■ **RECOMMENDATION 5**
Patients with GD who are at increased risk for complications due to worsening of hyperthyroidism (i.e., those who are extremely symptomatic or have free T_4 estimates 2–3 times the upper limit of normal) should be treated with beta-adrenergic blockade prior to radioactive iodine therapy. **1/+00**

■ **RECOMMENDATION 6**
Pretreatment with methimazole prior to radioactive iodine therapy for GD should be considered in patients who are at increased risk for complications due to worsening of hyperthyroidism (i.e., those who are extremely symptomatic or have free T_4 estimate 2–3 times the upper limit of normal). **2/+00**
Task force opinion was not unanimous; one person held the opinion that pretreatment with methimazole is not necessary in this setting.

■ **RECOMMENDATION 7**
Medical therapy of any comorbid conditions should be optimized prior to administering radioactive iodine. **1/+00**

^{131}I has been used to treat hyperthyroidism for six decades. This therapy is well tolerated and complications are rare, except for those related to ophthalmopathy (see section [T].) Thyroid storm occurs only rarely following the administration of radioactive iodine (50,51). In one study of patients with thyrotoxic cardiac disease treated with radioactive iodine as the sole modality, no clinical worsening in any of the cardinal symptoms of thyrotoxicosis was seen (52). The frequency of short-term worsening of hyperthyroidism following pretreatment with ATD therapy is not known. However, the use of methimazole (MMI) or carbimazole, the latter of which is not marketed in the United States, before and after ^{131}I treatment may be considered in patients with severe thyrotoxicosis (i.e., those

who are extremely symptomatic or have free T_4 estimates 2–3 times the upper limit of normal), the elderly, and those with substantial comorbidity that puts them at greater risk for complications of worsening hyperthyroidism (53,54). The latter includes patients with cardiovascular complications such as atrial fibrillation, heart failure, or pulmonary hypertension and those with renal failure, infection, trauma, poorly controlled diabetes mellitus, and cerebrovascular or pulmonary disease (50). These comorbid conditions should be addressed with standard medical care and the patient rendered medically stable before the administration of radioactive iodine. In addition, beta-adrenergic blocking drugs should be used judiciously in these patients in preparation for radioiodine therapy (20,55).

One committee member felt that MMI use is not necessary in preparation, as there is insufficient evidence for radioactive iodine worsening either the clinical or biochemical aspects of hyperthyroidism, and it only delays treatment with radioactive iodine. In addition, there is evidence that MMI pretreatment may reduce the efficacy of subsequent radioactive iodine therapy (6,52,56).

Technical remarks: If given as pretreatment, MMI should be discontinued 3–5 days before the administration of radioactive iodine, restarted 3–7 days later, and generally tapered over 4–6 weeks as thyroid function normalizes. Over several decades, there have been reports that pretreatment with lithium reduces the activity of ^{131}I necessary for cure of Graves' hyperthyroidism and may prevent the thyroid hormone increase seen upon ATD withdrawal (57–59). However, this is not used widely, and there is insufficient evidence to recommend the practice.

[D2] Administration of ^{131}I in the treatment of GD

■ **RECOMMENDATION 8**

Sufficient radiation should be administered in a single dose (typically 10–15 mCi) to render the patient with GD hypothyroid. **1/++0**

■ **RECOMMENDATION 9**

A pregnancy test should be obtained within 48 hours prior to treatment in any female with childbearing potential who is to be treated with radioactive iodine. The treating physician should obtain this test and verify a negative result prior to administering radioactive iodine. **1/+00**

The goal of ^{131}I is to control hyperthyroidism by rendering the patient hypothyroid; this treatment is very effective, provided sufficient radiation is deposited in the thyroid. This can be accomplished equally well by either administering a fixed activity or by calculating the activity based on the size of the thyroid and its ability to trap iodine (44). The first method is simple, and there is evidence that 10 mCi (370 MBq) results in hypothyroidism in 69% (representing cure) at 1 year (60) and 15 mCi (450 MBq) results in hypothyroidism in 75% at 6 months (61). The second method requires three unknowns to be determined: the uptake of radioactive iodine, the size of the thyroid, and the quantity of radiation (μCi or Bq) to be deposited per gram (or cc) of thyroid (e.g., activity (μCi) = gland weight (g) × 150 μCi/g × [1/24 hour uptake on% of dose]). The activity in μCi is converted to mCi by dividing the result by 1000. The most frequently used uptake is calculated at 24 hours, and the size of the thyroid is determined by palpation or ultrasound. One study found that this estimate by experienced physicians is accurate compared with anatomic imaging (62); however, other investigators have not confirmed this observation (63). There is wide variation in the recommended quantity of ^{131}I that should be deposited (i.e., between 50 and 200 μCi/g). Historically, activities at the low end of the spectrum have led to a higher proportion of treatment failures (41).

Alternately, a more detailed calculation can be made to deposit a specific number of radiation absorbed dose (rad) or Gy to the thyroid. Using this approach, it is also necessary to know the effective half-life of the ^{131}I (44). This requires additional time and computation and, because the outcome is not better, this method is seldom used in the United States. Evidence shows that to achieve a hypothyroid state, >150 μCi/g needs to be delivered (61,64,65). Patients who are on dialysis or who have jejunostomy or gastric feeding tubes require special care when being administered therapeutic doses of radioiodine (66).

Propylthiouracil (PTU) treatment before ^{131}I increases the radioresistance of the thyroid (51,67). Whether MMI may have the same effect is unclear (51). Use of higher activities of ^{131}I may offset the reduced effectiveness of ^{131}I therapy following antithyroid medication (53,54). A special diet is not required before radioactive iodine therapy, but excessive amounts of iodine, including iodine-containing multivitamins, should be avoided for at least 7 days. A low-iodine diet may be useful for those with relatively low RAIU to increase the proportion of radioactive iodine trapped.

A long-term increase in cardiovascular and cerebrovascular deaths has been reported after ^{131}I therapy, likely due to the hyperthyroidism rather than the treatment (56). While this study also found a small increase in cancer mortality, long-term studies of larger numbers of patients have not shown a statistically significant increase in cancer deaths following this treatment (68–74). In some men, there is a modest fall in the testosterone to luteinizing hormone (LH) ratio after ^{131}I therapy that is subclinical and reversible (75). Conception should be delayed for 4–6 months in women to assure stable euthyroidism (on thyroid hormone replacement following successful thyroid ablation) and 3–4 months in men to allow for turnover of sperm production. However, once the patient (both genders) is euthyroid,

there is no evidence of reduced fertility and offspring of treated patients show no congenital anomalies compared to the population at large.

Technical remarks: Rendering the patient hypothyroid can be accomplished equally well by administering either a sufficient fixed activity or calculating an activity based on the size of the thyroid and its ability to trap iodine. Fetuses exposed to ^{131}I after the 10th to 11th week of gestation may be born athyreotic (76,77) and are also at a theoretical increased risk for reduced intelligence and/or cancer. In breast-feeding women, radioactive iodine therapy should not be administered for at least 6 weeks after lactation stops to ensure that the radioactivity will no longer be actively concentrated in the breast tissues.

■ **RECOMMENDATION 10**

The physician administering the radioactive iodine should provide written advice concerning radiation safety precautions following treatment. If the precautions cannot be followed, alternative therapy should be selected. **1/+00**

All national and regional radiation protection rules regarding radioactive iodine treatment should be followed (78). In the United States, the treating physician must ensure and document that no adult member of the public is exposed to 0.5 mSv (500 milli-roentgen equivalent in man [mrem]) when the patient is discharged with a retained activity of 33 mCi (1.22 GBq) or greater, or emits ≥7 mrem/h (70 μSv/h) at 1 m.

Technical remarks: Continuity of follow-up should be provided and can be facilitated by written communication between the referring physician and the treating physician, including a request for therapy from the former and a statement from the latter that the treatment has been administered.

[D3] Patient follow-up after ^{131}I therapy for GD

■ **RECOMMENDATION 11**

Follow-up within the first 1–2 months after radioactive iodine therapy for GD should include an assessment of free T_4 and total T_3. If the patient remains thyrotoxic, biochemical monitoring should be continued at 4–6 week intervals. **1/+00**

Most patients respond to radioactive iodine therapy with a normalization of thyroid function tests and clinical symptoms within 4–8 weeks. Hypothyroidism may occur from 4 weeks on, but more commonly between 2 and 6 months, and the timing of thyroid hormone replacement therapy should be determined by results of thyroid function tests, clinical symptoms, and physical examination. Transient hypothyroidism following radioactive iodine therapy can rarely occur, with subsequent complete recovery of thyroid function or recurrent hyperthyroidism (79). When thyroid hormone replacement is initiated, the dose should be adjusted based on an assessment of free T_4. The required dose may be less than the typical full replacement, and careful titration is necessary owing to nonsuppressible residual thyroid function. Overt hypothyroidism should be avoided, especially in patients with active GO (see section T2). Once euthyroidism is achieved, lifelong annual thyroid function testing is recommended.

Technical remarks: Since TSH levels may remain suppressed for a month or longer after hyperthyroidism resolves, the levels should be interpreted cautiously and only in concert with free T_4 and T_3 estimates.

[D4] Treatment of persistent Graves' hyperthyroidism following radioactive iodine therapy

■ **RECOMMENDATION 12**

When hyperthyroidism due to GD persists after 6 months following ^{131}I therapy, or if there is minimal response 3 months after therapy, retreatment with ^{131}I is suggested. **2/+00**

Technical remarks: Response to radioactive iodine can be assessed by monitoring the size of the gland, thyroid function, and clinical signs and symptoms. The goal of retreatment is to control hyperthyroidism with certainty by rendering the patient hypothyroid. Patients who have persistent, suppressed TSH with normal total T_3 and free T_4 estimates may not require immediate retreatment but should be monitored closely for either relapse or development of hypothyroidism. In the small percentage of patients with hyperthyroidism refractory to several applications of ^{131}I, surgery could be considered (80).

[E] If antithyroid drugs are chosen as initial management of GD, how should the therapy be managed?

ATDs have been employed for six decades (81). The goal of the therapy is to render the patient euthyroid as quickly and safely as possible. These medications do not cure Graves' hyperthyroidism. However, when given in adequate doses, they are very effective in controlling the hyperthyroidism; when they fail to achieve euthyroidism, the usual cause is nonadherence (82). The treatment might have a beneficial immunosuppressive role, but the major effect is to reduce the production of thyroid hormones and maintain a euthyroid state while awaiting a spontaneous remission.

[E1] Initiation of antithyroid drug therapy for the treatment of GD

■ **RECOMMENDATION 13**

Methimazole should be used in virtually every patient who chooses antithyroid drug therapy for GD, except during the first trimester of pregnancy when propylthiouracil is preferred, in the treatment of thyroid storm, and in patients with minor reactions to methimazole who refuse radioactive iodine therapy or surgery. **1/++0**

■ **RECOMMENDATION 14**

Patients should be informed of side effects of antithyroid drugs and the necessity of informing the physician promptly if they should develop pruritic rash, jaundice, acolic stools or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, or pharyngitis. Before starting antithyroid drugs and at each subsequent visit, the patient should be alerted to stop the medication immediately and call their physician when there are symptoms suggestive of agranulocytosis or hepatic injury. **1/+00**

■ **RECOMMENDATION 15**

Prior to initiating antithyroid drug therapy for GD, we suggest that patients have a baseline complete blood count, including white count with differential, and a liver profile including bilirubin and transaminases. **2/+00**

In the United States, MMI and PTU are available, and in some countries, carbimazole, a precursor of MMI, is widely used. MMI and carbimazole, which is rapidly converted to MMI in the serum (10 mg of carbimazole is metabolized to approximately 6 mg of MMI), work in a virtually identical fashion and will both be referred to as MMI in this text. Both are effective as a single daily dose. At the start of MMI therapy, higher doses are advised (10–20 mg daily) to restore euthyroidism, following which the dose can be titrated to a maintenance level (generally 5–10 mg daily) (81,83). MMI has the benefit of once-a-day administration and a reduced risk of major side effects compared to PTU. PTU has a shorter duration of action and is usually administered two or three times daily, starting with 50–150 mg three times daily, depending on the severity of the hyperthyroidism. As the clinical findings and thyroid function tests return to normal, reduction to a maintenance PTU dose of 50 mg two or three times daily is usually possible. Higher doses of antithyroid medication are sometimes administered continuously and combined with L-thyroxine in doses to maintain euthyroid levels (so-called block and replace therapy). However, this approach is not generally recommended, as it has been shown to result in a higher rate of ATD side effects (81,84).

PTU may rarely cause agranulocytosis, whereas low doses of MMI may be less likely to do so (85,86). PTU very infrequently causes antineutrophil cytoplasmic antibody (ANCA)-positive small vessel vasculitis (87,88), with a risk that appears to increase with time as opposed to other adverse effects seen with ATDs that typically occur early in the course of treatment (89,90). PTU can cause fulminant hepatic necrosis that may be fatal; liver transplantation has been necessary in some patients taking PTU (91). It is for this reason that the FDA recently issued a safety alert regarding the use of PTU, noting that 32 (22 adult and 10 pediatric) cases of serious liver injury have been associated with PTU use (92,93).

MMI hepatotoxicity is typically cholestatic, but hepatocellular disease may rarely be seen (94,95). Aplasia cutis of the scalp is rarely found in babies born to mothers taking MMI (96). MMI taken by the mother in the first trimester is also associated with a syndrome of MMI embryopathy, including choanal and esophageal atresia (97,98). Arthropathy and a lupus-like syndrome rarely can occur with either MMI or PTU.

Technical remarks: Baseline blood tests to aid in the interpretation of future laboratory values should be considered before initiating antithyroid drug therapy. This is suggested in part because low white cell counts are common in patients with autoimmune diseases and in African Americans, and abnormal liver enzymes are frequently seen in patients with thyrotoxicosis. In addition, a baseline absolute neutrophil count <500/mm^3 or liver transaminase enzyme levels elevated more than fivefold the upper limit of normal are contraindications to initiating antithyroid drug therapy. It is advisable to provide information concerning side effects of ATDs to the patient both verbally and in writing to assure their comprehension, and document that this has been done. This information can be found on the UpToDate Web site (99).

[E2] Monitoring of patients taking antithyroid drugs

There is a need for periodic clinical and biochemical evaluation of thyroid status in patients taking ATDs, and it is essential that the patient understand its importance. An assessment of serum free T_4 should be obtained about 4 weeks after initiation of therapy, and the dose of medication adjusted accordingly. Serum T_3 also may be monitored, since the estimated serum free T_4 levels may normalize with persistent elevation of serum T_3. Appropriate monitoring intervals are every 4–8 weeks until euthyroid levels are achieved with the minimal dose of medication. Once the patient is euthyroid, biochemical testing and clinical evaluation can be undertaken at intervals of 2–3 months. An assessment of serum free T_4 and TSH are required before treatment and at intervals after starting the treatment. Serum TSH may remain suppressed for several

months after starting therapy and is therefore not a good parameter to monitor therapy early in the course.

■ **RECOMMENDATION 16**
A differential white blood cell count should be obtained during febrile illness and at the onset of pharyngitis in all patients taking antithyroid medication. Routine monitoring of white blood counts is not recommended. **1/+00**

There is no consensus concerning the utility of periodic monitoring of white blood cell counts and liver function tests in predicting early onset of adverse reaction to the medication (100). While routine monitoring of white blood cell counts may detect early agranulocytosis, this practice is not likely to identify cases, as the frequency is quite low (0.2%–0.5%) and the condition sudden in onset. Because patients are typically symptomatic, measuring white blood cell counts during febrile illnesses and at the onset of pharyngitis has been the standard approach to monitoring. In a patient developing agranulocytosis or other serious side effects while taking either MMI or PTU, use of the other medication is absolutely contraindicated owing to risk of cross-reactivity between the two medications (101).

■ **RECOMMENDATION 17**
Liver function and hepatocellular integrity should be assessed in patients taking propylthiouracil who experience pruritic rash, jaundice, light-colored stool or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea, or fatigue. **1/+00**

Hyperthyroidism can itself cause mildly abnormal liver function tests, and PTU may cause transient elevations of serum transaminases in up to one-third of patients. Significant elevations to threefold above the upper limit of normal are seen in up to 4% of patients taking PTU (102), a prevalence higher than with MMI. As noted above, PTU can also cause fatal hepatic necrosis, leading to the suggestion by some that patients taking this ATD have routine monitoring of their liver function, especially during the first 6 months of therapy. It is difficult to distinguish these abnormalities from the effect of persistent thyrotoxicosis unless they are followed prospectively. In patients with improving thyrotoxicosis, a rising alkaline phosphatase with normalization of other liver function does not indicate worsening hepatic toxicity. The onset of PTU-induced hepatotoxicity may be acute, difficult to appreciate clinically, and rapidly progressive. If not recognized, it can lead to liver failure and death (92,103–105). Routine monitoring of liver function in all patients taking antithyroid medication has not been found to prevent severe hepatotoxicity.

Technical remarks: PTU should be discontinued if transaminase levels (either elevated at onset of therapy, found incidentally or measured as clinically indicated) reach 2–3 times the upper limit of normal and fail to improve within 1 week with repeat testing. After discontinuing the drug, liver function tests should be monitored weekly until there is evidence of resolution. If resolution is not evident, prompt referral to a gastroenterologist or hepatologist is warranted. Except in cases of severe PTU-induced hepatotoxicity, MMI can be used to control the thyrotoxicosis without ill effect (106,107).

[E3] Management of allergic reactions

■ **RECOMMENDATION 18**
Minor cutaneous reactions may be managed with concurrent antihistamine therapy without stopping the antithyroid drug. Persistent minor side effects of antithyroid medication should be managed by cessation of the medication and changing to radioactive iodine or surgery, or switching to the other antithyroid drug when radioactive iodine or surgery are not options. In the case of a serious allergic reaction, prescribing the alternative drug is not recommended. **1/+00**

Minor allergic side effects, such as a limited, minor rash, may occur in up to 5% of patients taking either MMI or PTU (81).

[E4] Duration of antithyroid drug therapy for GD

■ **RECOMMENDATION 19**
If methimazole is chosen as the primary therapy for GD, the medication should be continued for approximately 12–18 months, then tapered or discontinued if the TSH is normal at that time. **1/+++**

■ **RECOMMENDATION 20**
Measurement of TRAb levels prior to stopping antithyroid drug therapy is suggested, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating greater chance for remission. **2/+00**

■ **RECOMMENDATION 21**
If a patient with GD becomes hyperthyroid after completing a course of methimazole, consideration should be given to treatment with radioactive iodine or thyroidectomy. Low-dose methimazole treatment for longer than 12–18 months may be considered in patients not in remission who prefer this approach. **2/+00**

A patient is considered to be in remission if they have had a normal serum TSH, FT_4, and T_3 for 1 year after discontinuation of ATD therapy. The remission rate varies considerably between geographical areas. In the United States, about 20%–30% of patients will have a lasting

remission after 12–18 months of medication (44). The remission rate appears to be higher in Europe and Japan; a long-term European study indicated a 50%–60% remission rate after 5–6 years of treatment (108). A meta-analysis shows the remission rate in adults is not improved by a course of ATDs longer than 18 months (84). A lower remission rate has been described in men, smokers (especially men), and those with large goiters (≥80 g) (109–113). Persistently high levels of TRAb and high thyroid blood flow identified by color Doppler ultrasound are also associated with higher relapse rates (112,114–116), and these patients should be assessed more frequently and at shorter intervals after antithyroid drugs are discontinued. Conversely, patients with mild disease, small goiters, and negative TRAb have a remission rate over 50%, making the use of antithyroid medications potentially more favorable in this group of patients (117).

Technical remarks: When MMI is discontinued, thyroid function testing should continue to be monitored at 1–3-month intervals for 6–12 months to diagnose relapse early. The patient should be counseled to contact the treating physician if symptoms of hyperthyroidism are recognized.

[F] If thyroidectomy is chosen for treatment of GD, how should it be accomplished?

[F1] Preparation of patients with GD for thyroidectomy

■ **RECOMMENDATION 22**
Whenever possible, patients with GD undergoing thyroidectomy should be rendered euthyroid with methimazole. Potassium iodide should be given in the immediate preoperative period. **1/+00**

■ **RECOMMENDATION 23**
In exceptional circumstances, when it is not possible to render a patient with GD euthyroid prior to thyroidectomy, the need for thyroidectomy is urgent, or when the patient is allergic to antithyroid medication, the patient should be adequately treated with beta-blockade and potassium iodide in the immediate preoperative period. The surgeon and anesthesiologist should have experience in this situation. **1/+00**

Thyroid storm may be precipitated by the stress of surgery, anesthesia, or thyroid manipulation and may be prevented by pretreatment with ATDs. Whenever possible, thyrotoxic patients who are undergoing thyroidectomy should be rendered euthyroid by MMI before undergoing surgery. Preoperative potassium iodide, saturated solution of potassium iodide (SSKI) or inorganic iodine, should be used before surgery in most patients with GD. This treatment is beneficial as it decreases thyroid blood flow, vascularity, and intraoperative blood loss during thyroidectomy (118,119). In addition, rapid preparation for emergent surgery can be facilitated by the use of corticosteroids (120).

Technical remarks: Potassium iodide can be given as 5–7 drops (0.25–0.35 mL) Lugol's solution (8 mg iodide/drop) or 1–2 drops (0.05–0.1 mL) SSKI (50 mg iodide/drop) three times daily mixed in water or juice for 10 days before surgery.

[F2] The surgical procedure and choice of surgeon

■ **RECOMMENDATION 24**
If surgery is chosen as the primary therapy for GD, near-total or total thyroidectomy is the procedure of choice. **1/++0**

Thyroidectomy has a high cure rate for the hyperthyroidism of GD. Total thyroidectomy has a nearly 0% risk of recurrence, whereas subtotal thyroidectomy may have an 8% chance of persistence or recurrence of hyperthyroidism at 5 years (121).

The most common complications following near-total or total thyroidectomy are hypocalcemia (which can be transient or permanent), recurrent or superior laryngeal nerve injury (which can be temporary or permanent), postoperative bleeding, and complications related to general anesthesia.

■ **RECOMMENDATION 25**
If surgery is chosen as the primary therapy for GD, the patient should be referred to a high-volume thyroid surgeon. **1/++0**

Improved patient outcome has been shown to be independently associated with high thyroidectomy surgeon volume; specifically, complication rate, length of hospital stay, and cost are reduced when the operation is performed by a surgeon who conducts many thyroidectomies. A significant association is seen between increasing thyroidectomy volume and improved patient outcome; the association is robust and is more pronounced with an increasing number of thyroidectomies (122,123).

The surgeon should be thoroughly trained in the procedure, have an active practice in thyroid surgery, and have conducted a significant number of thyroidectomies with a low frequency of complications. There is a robust, statistically significant association between increasing surgeon volume and superior patient outcomes for thyroidectomy. Data show that surgeons who perform more than 30 thyroid surgeries per year have superior patient clinical and economic outcomes compared to those who perform fewer, and surgeons who perform at least 100 per year have still better outcomes (46,123). Following thyroidectomy for

GD in the hands of high-volume thyroid surgeons, the rate of permanent hypocalcemia has been determined to be <2%, and permanent recurrent laryngeal nerve (RLN) injury occurs in <1% (124). The frequency of bleeding necessitating reoperation is 0.3%–0.7% (125). Mortality following thyroidectomy is between 1 in 10,000 and 5 in 1,000,000 (126).

[F3] Postoperative care

■ **RECOMMENDATION 26**
Following thyroidectomy for GD, we suggest that serum calcium or intact parathyroid hormone levels be measured, and that oral calcium and calcitriol supplementation be administered based on these results. **2/+00**

Successful prediction of calcium status after total thyroidectomy can be achieved using the slope of 6- and 12-hour postoperative calcium levels or the postoperative intact parathyroid hormone (iPTH) level (127–132). Patients can be discharged if they are asymptomatic and their serum calcium levels are 7.8 mg/dL (1.95 mmol/L) or above and are not falling (133). The use of ionized calcium measurements (or serum calcium corrected for albumin level) are preferred by some, and are essential if the patient has abnormal levels of serum proteins. Low iPTH levels (<10–15 pg/mL) in the immediate postoperative setting appear to predict symptomatic hypocalcemia and need for calcium and calcitriol (1,25 vitamin D) supplementation (134,135).

Postoperative routine supplementation with oral calcium and calcitriol decreases development of hypocalcemic symptoms and intravenous calcium requirement, allowing for safer early discharge (136). Intravenous calcium gluconate should be readily available and may be administered if patients have worsening hypocalcemic symptoms despite oral supplementation and/or their concomitant serum calcium levels are falling despite oral repletion. Persistent hypocalcemia in the postoperative period should prompt measurement of serum magnesium and possible magnesium repletion (137,138). Following discharge, serum iPTH levels should be measured in the setting of persistent hypocalcemia to determine if permanent hypoparathyroidism is truly present or whether "bone hunger" is ongoing. If the level of circulating iPTH is appropriate for the level of serum calcium, calcium and calcitriol therapy can be tapered.

Technical remarks: Prophylactic calcium supplementation can be accomplished with oral calcium (usually calcium carbonate, 1250–2500 mg) four times daily, tapered by 500 mg every 2 days, or 1000 mg every 4 days as tolerated. In addition, calcitriol may be started at a dose of 0.5 mcg daily and continued for 1–2 weeks (133) and increased or tapered according to the calcium and/or iPTH level. Patients can be discharged if they are asymptomatic and have stable serum calcium levels. Postoperative evaluation is generally conducted 1–2 weeks following dismissal with continuation of supplementation based on clinical parameters.

■ **RECOMMENDATION 27**
Antithyroid drugs should be stopped at the time of thyroidectomy for GD, and beta-adrenergic blockers should be weaned following surgery. **1/+00**

■ **RECOMMENDATION 28**
Following thyroidectomy for GD, L-thyroxine should be started at a daily dose appropriate for the patient's weight (0.8 μg/lb or 1.7 μg/kg), and serum TSH measured 6–8 weeks postoperatively. **1/+00**

Technical remarks: Once stable and normal, TSH should be measured annually or more frequently if clinically indicated.

[G] How should thyroid nodules be managed in patients with GD?

■ **RECOMMENDATION 29**
If a thyroid nodule is discovered in a patient with GD, the nodule should be evaluated and managed according to recently published guidelines regarding thyroid nodules in euthyroid individuals. **1/++0**

Thyroid cancer occurs in GD with a frequency of 2% or less (139). Thyroid nodules larger than 1–1.5 cm should be evaluated before radioactive iodine therapy. If a radioactive iodine scan is performed, any nonfunctioning or hypofunctioning nodules should be considered for fine needle aspiration (FNA), as these may have a higher probability of being malignant (46). If the cytopathology is indeterminate (suspicious) or is diagnostic of malignancy, surgery is advised after normalization of thyroid function with ATDs. Disease-free survival at 20 years is reported to be 99% after thyroidectomy for GD in patients with small (≤1 cm) coexisting thyroid cancers (140).

The use of thyroid ultrasonography in all patients with GD has been shown to identify more nodules and cancer than does palpation and ^{123}I scintigraphy. However, since most of these cancers are papillary microcarcinomas with minimal clinical impact, further study is required before routine ultrasound (and therefore surgery) can be recommended (141,142).

Technical remarks: Both the ATA and AACE, the latter in conjunction with the European Thyroid Association

and Associazione Medici Endocrinologi, have recently published updated management guidelines for patients with thyroid nodules (143,144).

[H] How should thyroid storm be managed?

■ **RECOMMENDATION 30**

A multimodality treatment approach to patients with thyroid storm should be used, including beta-adrenergic blockade, antithyroid drug therapy, inorganic iodide, corticosteroid therapy, aggressive cooling with acetaminophen and cooling blankets, volume resuscitation, respiratory support and monitoring in an intensive care unit. **1/+00**

Life-threatening thyrotoxicosis or thyroid storm is a rare, occasionally iatrogenic disorder characterized by multisystem involvement and a high mortality rate if not immediately recognized and treated aggressively (20). A high index of suspicion for thyroid storm should be maintained in patients with thyrotoxicosis associated with any evidence of systemic decompensation. Precise criteria for thyroid storm have been defined (Table 5) (21) and include tachycardia, arrhythmias, congestive heart failure, hypotension, hyperpyrexia, agitation, delirium, psychosis, stupor and coma, as well as nausea, vomiting, diarrhea, and hepatic failure. Precipitants of thyroid storm in a patient with previously compensated thyrotoxicosis include abrupt cessation of antithyroid drugs, thyroid, or nonthyroidal surgery in a patient with unrecognized or inadequately treated thyrotoxicosis, and a number of acute illnesses unrelated to thyroid disease (145). Thyroid storm also occurs rarely following radioactive iodine therapy. Exposure to iodine from the use of iodine-containing contrast agents may be an additional factor in the development of thyroid storm in patients with illnesses unrelated to thyroid disease. Each pharmacologically accessible step in thyroid hormone production and action is targeted in the treatment of patients with thyroid storm (Table 6).

Table 5. Point Scale for the Diagnosis of Thyroid Storm

Criteria	*Points*	*Criteria*	*Points*
Thermoregulatory dysfunction		**Gastrointestinal-hepatic dysfunction**	
Temperature (°F)		Manifestation	
99.0–99.9	5	Absent	0
100.0–100.9	10	Moderate (diarrhea, abdominal pain, nausea/vomiting)	10
101.0–101.9	15	Severe (jaundice)	20
102.0–102.9	20		
103.0–103.9	25		
≥104.0	30		
Cardiovascular		**Central nervous system disturbance**	
Tachycardia (beats per minute)		Manifestation	
100–109	5	Absent	0
110–119	10	Mild (agitation)	10
120–129	15	Moderate (delirium, psychosis, extreme lethargy)	20
130–139	20	Severe (seizure, coma)	30
≥140	25		
Atrial fibrillation			
Absent	0		
Present	10		
Congestive heart failure		**Precipitant history**	
Absent	0	Status	
Mild	5	Positive	0
Moderate	10	Negative	10
Severe	20		
Scores totaled			
>45	Thyroid storm		
25–44	Impending storm		
<25	Storm unlikely		

Source: Burch and Wartofsky, 1993 (21). Printed with permission.

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Table 6. Thyroid Storm: Drugs and Doses

Drug	*Dosing*	*Comment*
Propylthiouracil[a]	500–1000 mg load, then 250 mg every 4 hours	Blocks new hormone synthesis Blocks T_4-to-T_3 conversion
Methimazole	60–80 mg/day	Blocks new hormone synthesis
Propranolol	60–80 mg every 4 hours	Consider invasive monitoring in congestive heart failure patients Blocks T_4-to-T_3 conversion in high doses Alternate drug: esmolol infusion
Iodine (saturated solution of potassium iodide)	5 drops (0.25 mL or 250 mg) orally every 6 hours	Do not start until 1 hour after antithyroid drugs Blocks new hormone synthesis Blocks thyroid hormone release
Hydrocortisone	300 mg intravenous load, then 100 mg every 8 hours	May block T_4-to-T_3 conversion Prophylaxis against relative adrenal insufficiency Alternative drug: dexamethasone

[a]May be given intravenously.

Technical remarks: Treatment with inorganic iodine (SSKI/Lugol's solution, or oral radiographic contrast) leads to rapid decreases in both T_4 and T_3 levels and combined with antithyroid medication, results in rapid control of Graves' hyperthyroidism, and can aid in severely thyrotoxic patients (146). Unfortunately, the oral radiographic contrast agents ipodate and iopanoic acid are not currently available in many countries.

[I] How should overt hyperthyroidism due to TMNG or TA be managed?

■ **RECOMMENDATION 31**

We suggest that patients with overtly TMNG or TA be treated with either ^{131}I therapy or thyroidectomy. On occasion, long-term, low-dose treatment with methimazole may be appropriate. **2/++0**

There are two effective and relatively safe treatment options, ^{131}I therapy and thyroidectomy. The decision regarding treatment should take into consideration a number of clinical and demographic factors, as well as patient preference. The goal of therapy is the rapid and durable elimination of the hyperthyroid state.

For patients with TMNG, the risk of treatment failure or need for repeat treatment is <1% following near-total/total thyroidectomy (147,148), compared with a 20% risk of the need for retreatment following ^{131}I therapy (147,149). Euthyroidism without the need for antithyroid drug therapy is achieved within days after surgery (147,148); after radioactive iodine, the response is 50%–60% by 3 months, and 80% by 6 months (147,149). On the other hand, the risk of hypothyroidism and the requirement for exogenous thyroid hormone therapy is 100% after near-total/total thyroidectomy. In a large study of patients with TMNG treated with ^{131}I, the prevalence of hypothyroidism was 3% at 1 year and 64% at 24 years (150). Hypothyroidism was more common among patients under 50 years of age (61% after 16 years), compared with those over 70 years (36% after 16 years).

For patients with TA, the risk of treatment failure is <1% after surgical resection (ipsilateral thyroid lobectomy or isthmusectomy) (151), whereas following ^{131}I there is a 6%–18% risk of persistent hyperthyroidism and a 5.5% risk of recurrent hyperthyroidism (152). Typically, euthyroidism without the need for antithyroid drug therapy is achieved within days after surgery. There is a 75% response rate by 3 months following ^{131}I therapy for TA (152). The prevalence of hypothyroidism is 2.3% following lobectomy for TA (151,153), and lower after isthmusectomy in the unique circumstance where the TA is confined to the thyroid isthmus. In contrast, the prevalence of hypothyroidism after radioactive iodine is progressive and hastened by the presence of antithyroid antibodies or a nonsuppressed TSH at the time of treatment (152,154,155). A study following 684 patients with TA treated with ^{131}I reported a progressive increase in overt and subclinical hypothyroidism (154). At 1 year, the investigators noted a 7.6% prevalence, with 28% at 5 years, 46% at 10 years, and 60% at 20 years. They observed a faster progression to hypothyroidism among patients who were older and who had incomplete TSH suppression (correlating with only partial extranodular parenchymal suppression) due to prior therapy with ATDs.

In large retrospective series of patients with TMNG presenting with compressive symptoms, all patients undergoing total thyroidectomy had resolution of these symptoms after treatment, whereas only 46% of patients

undergoing radioactive iodine had improvement in such symptoms (156). This may be due in part to the fact that very large goiters treated with high-activity radioactive iodine only decrease in size by 30%–50% (157). The nodule is rarely eradicated in patients with TA undergoing ^{131}I therapy, which can lead to the need for continued surveillance (152,155).

Potential complications following near-total/total thyroidectomy include the risk of permanent hypoparathyroidism (<2.0%) or RLN injury (<2.0%) (158,159). There is a small risk of permanent RLN injury with surgery for TA (151). Following ^{131}I therapy, there have been reports of new-onset GD (up to 4% prevalence) (160), as well as concern for thyroid malignancy (68) and a very minimal increase in late nonthyroid malignancy (161).

Technical remarks: Once the diagnosis has been made, the treating physician and patient should discuss each of the treatment options, including the logistics, benefits, expected speed of recovery, drawbacks, side effects, and costs. This sets the stage for the physician to make a recommendation based upon best clinical judgment and for the final decision to incorporate the personal values and preferences of the patient.

Factors that favor a particular modality as treatment for TMNG or TA:

a. ^{131}I: Advanced patient age, significant comorbidity, prior surgery or scarring in the anterior neck, small goiter size, RAIU sufficient to allow therapy, and lack of access to a high-volume thyroid surgeon (the latter factor is more important for TMNG than for TA).
b. Surgery: Presence of symptoms or signs of compression within the neck, concern for coexisting thyroid cancer, coexisting hyperparathyroidism requiring surgery, large goiter size (>80 g), substernal or retrosternal extension, RAIU insufficient for therapy, or need for rapid correction of the thyrotoxic state (156).

Contraindications to a particular modality as treatment for TNMG or TA:

a. ^{131}I: Definite contraindications to the use of radioactive iodine include pregnancy, lactation, coexisting thyroid cancer, individuals unable to comply with radiation safety guidelines, and females planning a pregnancy within 4–6 months.
b. Surgery: Factors weighing against the choice of surgery include significant comorbidity such as cardiopulmonary disease, end-stage cancer, or other debilitating disorders. Pregnancy is a relative contraindication and should only be used in this circumstance when rapid control of hyperthyroidism is required and antithyroid medications cannot be used. Thyroidectomy is best avoided in the first and third trimesters of pregnancy because of teratogenic effects associated with anesthetic agents and increased risk of fetal loss in the first trimester, and increased risk of preterm labor in the third. Optimally, thyroidectomy should be performed in the latter portion of the second trimester. Although it is the safest time, it is not without risk (4.5%–5.5% risk of preterm labor) (47,48).

Factors that may impact patient preference:

a. ^{131}I: Patients with either TMNG or TA choosing ^{131}I therapy would likely place relatively higher value on the avoidance of surgery and attendant hospitalization or complications arising from either surgery or anesthesia; also, patients with TMNG would place greater value on the possibility of remaining euthyroid after ^{131}I.
b. Surgery: Patients choosing surgery would likely place a relatively higher value on prompt and definitive control of hyperthyroid symptoms and avoidance of exposure to radioactivity and a lower value on potential surgical and anesthetic risks; patients with TA who choose surgery would place greater value on the possibility of achieving euthyroidism without hormone replacement, whereas patients with TMNG choosing surgery would place a lower value on the certain need for lifelong thyroid hormone replacement.

[J] If ^{131}I therapy is chosen, how should it be accomplished?

[J1] Preparation of patients with TMNG or TA for ^{131}I therapy

■ **RECOMMENDATION 32**

Patients with TMNG or TA who are at increased risk for complications due to worsening of hyperthyroidism, including the elderly and those with cardiovascular disease or severe hyperthyroidism, should be treated with beta-blockade prior to radioactive iodine therapy and until euthyroidism has been achieved. **1/+00**

Medical management before ^{131}I therapy should be tailored to the vulnerability of the patient based on the severity of the hyperthyroidism, patient age, and comorbid conditions. Worsened chemical hyperthyroidism with increased heart rate and rare cases of supraventricular tachycardia, including atrial fibrillation and atrial flutter,

have been observed in patients treated with ^{131}I for either TMNG or nontoxic multindoular goiter (MNG) (162–164). In susceptible patients with pre-existing cardiac disease or in the elderly, this may produce significant clinical worsening (163). Therefore, the use of beta-blockers to prevent post-treatment tachyarrhythmias should be considered in all patients with TMNG or TA who are older than 60 years of age and those with cardiovascular disease or severe hyperthyroidism (26). The decision regarding the use of MMI pretreatment is more complex and is discussed below.

■ **RECOMMENDATION 33**

Pretreatment with methimazole prior to radioactive iodine therapy for TMNG or TA should be considered in patients who are at increased risk for complications due to worsening of hyperthyroidism, including the elderly and those with cardiovascular disease or severe hyperthyroidism. **2/+00**

Task force opinion was not unanimous; one member held the opinion that pretreatment with methimazole in patients already treated with beta adrenergic blockade is not indicated in this setting.

The minority position regarding the above recommendation held that pretreating TMNG patients with MMI before radioactive iodine therapy is not necessary and delays the time to definitive treatment and cure. Beta-blockade alone was thought to be sufficient to prevent the majority of adverse events related to worsening of chemical hyperthyroidism that can occur following ^{131}I treatment for TMNG. Young and middle-aged patients with TMNG or TA generally do not require pretreatment with ATDs (MMI) before receiving radioactive iodine, but may benefit from beta-blockade if symptoms warrant and contraindications do not exist.

Technical remarks: If methimazole is used in preparation for radioactive iodine therapy in patients with TNMG or TA, caution should be taken to avoid radioiodine therapy when the TSH is normal or elevated to prevent direct ^{131}I treatment of perinodular and contralateral normal thyroid tissue, which increases the risk of developing hypothyroidism.

[J2] Evaluation of thyroid nodules before radioactive iodine therapy

■ **RECOMMENDATION 34**

Nonfunctioning nodules on radionuclide scintigraphy or nodules with suspicious ultrasound characteristics should be managed according to recently published guidelines regarding thyroid nodules in euthyroid individuals. **1/++0**

Thorough assessment of suspicious nodules within a TMNG, according to the recently published guidelines (143,144), should be completed before selection of radioactive iodine as the treatment of choice. The prevalence of thyroid cancer in TMNG historically has been estimated to be about 3% (148). More recently, it has been estimated to be as high as 9%, which is similar to the 10.6% prevalence noted in nontoxic MNG (165).

Technical remarks: Both the ATA and AACE, the latter in conjunction with the European Thyroid Association and Associazione Medici Endocrinologi, have recently published updated management guidelines for patients with thyroid nodules (143,144).

[J3] Administration of radioactive iodine in the treatment of TMNG or TA

■ **RECOMMENDATION 35**

For radioactive iodine treatment of TMNG, sufficient radiation should be administered in a single dose to alleviate hyperthyroidism. **1/++0**

The goal of radioactive iodine therapy, especially in older patients, is elimination of the hyperthyroid state. Higher activities of ^{131}I, even when appropriately calculated for the specific volume or mass of hyperthyroid tissue, result in more rapid resolution of hyperthyroidism and less need for retreatment, but a higher risk for early hypothyroidism. One study showed a 64% prevalence of hypothyroidism 24 years after radioactive iodine therapy for TMNG, with a higher prevalence among patients who required more than one treatment (150). The prevalence of hypothyroidism following ^{131}I therapy is increased by normalization or elevation of TSH at the time of treatment resulting from ATD pretreatment and by the presence of antithyroid antibodies (166).

The activity of radioiodine used to treat TMNG, calculated on the basis of goiter size to deliver 150–200 μCi per gram of tissue corrected for 24-hour RAIU, is usually higher than that needed to treat GD. In addition, the RAIU values for TMNG may be lower, necessitating an increase in the total dose of radioactive iodine. Radiation safety precautions may be onerous if high activities of ^{131}I are needed for large goiters. Pretreatment with MMI to a slightly elevated TSH increased RAIU enough to allow more efficacy from a fixed activity (30 mCi) of ^{131}I in a recent study of patients with TMNG (167). Use of recombinant human TSH is not indicated in TMNG due to risk of exacerbating the patient's hyperthyroidism (168).

Technical remarks: Swelling of the thyroid is very rare after ^{131}I treatment. However, patients should be advised to immediately report any tightening of the neck, difficulty breathing, or stridor following the administration of radioactive iodine. Any compressive symptoms, such as discomfort, swelling, dysphagia, or hoarseness, which develop

following radiotherapy, should be carefully assessed and monitored, and if clinically necessary, corticosteroids can be administered. Respiratory compromise in this setting is extremely rare and requires management as any other cause of acute tracheal compression.

■ **RECOMMENDATION 36**
For radioactive iodine treatment of TA, sufficient radiation to alleviate hyperthyroidism should be administered in a single dose. **1/++0**

Radioactive iodine administered to treat TA can be given either as a fixed activity (approximately 10–20 mCi) or an activity calculated on the basis of nodule size using 150–200 μCi ^{131}I per gram corrected for 24-hour RAIU (169). A long-term follow-up study of patients with TA, where patients with small (<4 cm) nodules were administered an average of 13 mCi and those with larger nodules an average of 17 mCi, showed a progressive increase in hypothyroidism over time in both groups, suggesting that hypothyroidism develops over time regardless of activity adjustment for nodule size (154). A randomized trial of 97 patients with TA compared the effects of high (22.5 mCi) or low (13 mCi) fixed activity radioactive iodine, with a calculated activity that was either high (180–200 μCi/g) or low (90–100 μCi/g) and corrected for 24-hour RAIU (169). This study confirmed previous reports showing an earlier disappearance of hyperthyroidism and earlier appearance of hypothyroidism with higher activity treatments. Use of a calculated activity allowed for a lower ^{131}I activity to be administered for a similar efficacy in the cure of hyperthyroidism.

[J4] Patient follow-up after ^{131}I therapy for TMNG or TA

■ **RECOMMENDATION 37**
Follow-up within the first 1–2 months after radioactive iodine therapy for TMNG or TA should include an assessment of free T_4, total T_3 and TSH. This should be repeated at 1–2 month intervals until stable results are obtained, then at least annually thereafter according to clinical indication. **1/+00**

Radioactive iodine therapy for TMNG results in resolution of hyperthyroidism in approximately 55% of patients at 3 months and 80% of patients at 6 months, with an average failure rate of 15% (147–149). Goiter volume is decreased by 3 months, with further reduction observed over 24 months, for a total size reduction of 40% (149). For TA, 75% of patients were no longer hyperthyroid at 3 months, with nodule volume decreased by 35% at 3 months and by 45% at 2 years (152). Risk of persistent or recurrent hyperthyroidism ranged from 0% to 30%, depending on the series (147–149,152). Long-term follow-up studies show a progressive risk of clinical or subclinical hypothyroidism of about 8% by 1 year and 60% by 20 years for TA (154), and an average of 3% by 1 year and 64% by 24 years for TMNG (150).

Technical remarks: If thyroid hormone therapy is necessary, the dose required may be less than full replacement due to underlying persistent autonomous thyroid function.

[J5] Treatment of persistent or recurrent hyperthyroidism following ^{131}I therapy for TMNG or TA

■ **RECOMMENDATION 38**
If hyperthyroidism persists beyond 6 months following ^{131}I therapy for TMNG or TA, retreatment with radioactive iodine is suggested. **2/+00**

Technical remarks: In severe or refractory cases of persistent hyperthyroidism due to TMNG or TA, surgery may be considered. As some patients with mild hyperthyroidism following radioactive iodine administration will continue to improve over time, use of MMI with close monitoring may be considered to allow control of the hyperthyroidism until the radioactive iodine is effective.

[K] If surgery is chosen, how should it be accomplished?

[K1] Preparation of patients with TMNG or TA for surgery

■ **RECOMMENDATION 39**
If surgery is chosen as treatment for TMNG or TA, patients with overt hyperthyroidism should be rendered euthyroid prior to the procedure with methimazole pretreatment (in the absence of allergy to the medication), with or without beta-adrenergic blockade. Preoperative iodine should not be used in this setting. **1/+00**

Risks of surgery are increased in the presence of thyrotoxicosis. Thyrotoxic crisis during or after the operation can result in extreme hypermetabolism, hyperthermia, tachycardia, hypertension, coma, or death. Therefore, prevention with careful preparation of the patient is of paramount importance (170,171). The literature reports a very low risk of anesthesia-related mortality associated with thyroidectomy (151,172). In patients who wish to avoid general anesthesia, or who have significant comorbidities, this risk can be lowered further when cervical block anesthesia with sedation is employed by thyroid surgeons and anesthesiologists experienced in this approach (173). However, this technique is not widely available in the U.S. Preoperative iodine therapy is not indicated due to risk of exacerbating the hyperthyroidism (174).

[K2] The surgical procedure and choice of surgeon

■ **RECOMMENDATION 40**
If surgery is chosen as treatment for TMNG, near- total or total thyroidectomy should be performed. **1/++0**

Recurrence can be avoided in TMNG if a near-total or total thyroidectomy is performed initially. This procedure can be performed with the same low rate of complications as a subtotal thyroidectomy (175–178). Reoperation for recurrent or persistant goiter results in a 3- to 10-fold increase in risk for permanent vocal cord paralysis or hypoparathyroidism (179,180).

■ **RECOMMENDATION 41**
Surgery for TMNG should be performed by a high-volume thyroid surgeon. **1/++0**

Data regarding outcomes following thyroidectomy in elderly patients have shown conflicting results. Overall, however, studies conducted at the population level have demonstrated significantly higher rates of postoperative complications, longer length of hospital stay, and higher costs among elderly patients (122). Data showing equivalent outcomes among the elderly usually have come from high-volume centers (181). There are robust data demonstrating that surgeon volume of thyroidectomies is an independent predictor of patient clinical and economic outcomes (i.e., in-hospital complications, length of stay, and total hospital charges) following thyroid surgery (122,123,182). There is a robust, statistically significant association between increasing surgeon volume and superior patient outcomes for thyroidectomy. Data show that surgeons who perform more than 30 thyroid surgeries per year have superior patient clinical and economic outcomes compared to those who perform fewer, and surgeons who perform at least 100 per year have still better outcomes. It is for this reason that near-total or total thyroidectomy for TMNG is best performed by a high-volume thyroid surgeon (123,181,182).

■ **RECOMMENDATION 42**
If surgery is chosen as the treatment for TA, an ipsilateral thyroid lobectomy, or isthmusectomy if the adenoma is in the thyroid isthmus, should be performed. **1/++0**

A preoperative thyroid ultrasound is useful, as it will detect the presence of contralateral nodularity that is suspicious in appearance or that will necessitate future surveillance, both circumstances in which a total thyroidectomy may be more appropriate. Lobectomy removes the TA while leaving normal thyroid tissue, allowing residual normal thyroid function in the majority of patients. One large clinical series for TA demonstrated no surgical deaths and low complication rates (151). Patients with positive antithyroid antibodies preoperatively have a higher risk of postoperative hypothyroidism (166).

■ **RECOMMENDATION 43**
We suggest that surgery for TA be performed by a high-volume surgeon. **2/++0**

While surgeon experience in the setting of TA is of somewhat less importance than in TMNG, it remains a factor to consider in deciding between surgery and radioactive iodine. High-volume thyroid surgeons tend to have better outcomes following lobectomy than low-volume surgeons, but the differences are not statistically significant (122).

[K3] Postoperative care

■ **RECOMMENDATION 44**
Following thyroidectomy for TMNG, we suggest that serum calcium or intact parathyroid hormone levels be measured, and that oral calcium and calcitriol supplementation be administered based on these results. **2/+00**

Technical remarks: The management of hypocalcemia following thyroidectomy for TMNG is essentially the same as that described in section F3 for postoperative management in GD. Severe or prolonged preoperative hyperthyroidism, and larger size and greater vascularity of the goiter (more typically seen in GD) increases the risks of postoperative hypocalcemia.

■ **RECOMMENDATION 45**
Methimazole should be stopped at the time of surgery for TMNG or TA. Beta-adrenergic blockade should be slowly discontinued following surgery. **1/+00**

■ **RECOMMENDATION 46**
Following surgery for TMNG, thyroid hormone replacement should be started at a dose appropriate for the patient's weight (0.8 mcg/lb or 1.7 mcg/kg) and age, with elderly patients needing somewhat less. TSH should be measured every 1–2 months until stable, and then annually. **1/+00**

Technical remarks: If a significant thyroid remnant remains following thyroidectomy, because such a remnant may demonstrate autonomous production of thyroid hormone, immediate postoperative doses of thyroid hormone should be initiated at somewhat less than full replacement doses and subsequently adjusted based on thyroid function testing.

■ **RECOMMENDATION 47**
Following surgery for TA, TSH and estimated free T_4 levels should be obtained 4–6 weeks after surgery, and thyroid hormone supplementation started if there is a persistent rise in TSH above the normal range. **1/+00**

Technical remarks: After lobectomy for TA, serum calcium levels do not need to be obtained, and calcium and calcitriol supplements do not need to be administered.

[K4] Treatment of persistent or recurrent disease following surgery for TMNG or TA

■ **RECOMMENDATION 48**
Radioactive iodine therapy should be used for retreatment of persistent or recurrent hyperthyroidism following inadequate surgery for TMNG or TA. **1/+00**

Persistent or recurrent hyperthyroidism following surgery is indicative of inadequate surgery. As remedial thyroid surgery comes at significantly increased risk of hypoparathyroidism and RLN injury, it should be avoided if possible in favor of radioactive iodine therapy (179,180). If this is not an option, it is essential that the surgery be performed by a high-volume thyroid surgeon.

[L] Is there a role for antithyroid drug therapy in patients with TMNG or TA?

ATDs do not induce remission in patients with nodular thyroid disease. Therefore, discontinuation of treatment results in relapse (117,159). However, prolonged (lifelong) ATD therapy may be the best choice for some individuals with limited longevity and increased surgical risk, including residents of nursing homes or other care facilities where compliance with radiation safety regulations may be difficult.

■ **RECOMMENDATION 49**
We suggest that long-term methimazole treatment of TMNG or TA be avoided, except in some elderly or otherwise ill patients with limited longevity who are able to be monitored regularly, and in patients who prefer this option. **2/+00**

Technical remarks: Because long-term, low-dose ATD treatment in nodular hyperthyroidism can be difficult to regulate, frequent (every 3 months) monitoring is recommended, especially in the elderly (183).

[M] Is there a role for radiofrequency, thermal, or alcohol ablation in the management of TA or TMNG?

Alternative techniques have been employed for the ablation of hyperfunctioning thyroid nodules; these include percutaneous ethanol injection (PEI) under sonographic guidance, as well as thermal and radiofrequency ablation. Data supporting the safety and efficacy of such techniques come largely from outside the United States (184–186). Long-term follow-up exists to 5 years, showing that PEI is effective and safe. In a large series of 125 patients, Tarantino *et al*. demonstrated an overall cure rate (absent uptake in the nodule) of 93%, and a major complication rate of 3% (184). These included transient laryngeal nerve damage, abscess, and hematoma. All patients remained euthyroid (low/normal TSH and normal free T_3 and free T_4 estimates) during follow-up. The average reduction in the volume of nodules after PEI was 66%. Given the relative lack of experience with these alternative techniques, ^{131}I therapy and surgery remain the mainstay of treatment. PEI or alternative treatments should be employed only in the very rare situation when standard therapies have failed, or are contraindicated or refused.

[N] How should GD be managed in children and adolescents?

[N1] General approach

■ **RECOMMENDATION 50**
Children with GD should be treated with methimazole, ^{131}I therapy, or thyroidectomy. ^{131}I therapy should be avoided in very young children (<5 years). ^{131}I therapy in patients between 5 and 10 years of age is acceptable if the calculated ^{131}I administered activity is <10 mCi. ^{131}I therapy in patients older than 10 years of age is acceptable if the activity is >150 μCi/g of thyroid tissue. Thyroidectomy should be chosen when definitive therapy is required, the child is too young for ^{131}I, and surgery can be performed by a high-volume thyroid surgeon. **1/++0**

The treatment of pediatric patients with GD varies considerably among institutions and practitioners. It is important to recognize that lasting remission after ATD therapy occurs in only a small minority of pediatric patients with GD, including children treated with ATDs for many years. In determining the initial treatment approach, the patient's age, clinical status, and likelihood of remission should be considered.

Because some children will go into remission, MMI therapy for 1–2 years is still considered first-line treatment for most children. However, the majority of pediatric patients with GD will eventually require either radioactive iodine or surgery. When ATDs are used in children, only MMI should be used, except in exceptional circumstances. If clinical characteristics suggest a low chance of remission at initial presentation, MMI, ^{131}I, or surgery may be considered initially. If remission is not achieved after a course of therapy with ATDs, ^{131}I or surgery should be considered.

Alternatively, MMI therapy may be continued until the child is considered old enough for surgery or radioactive iodine.

Properly administered, radioactive iodine is an effective treatment for GD in the pediatric population (187–189). ^{131}I is widely used in children, but still viewed as controversial by some practitioners owing primarily to concern over cancer risks (190). Although there are sparse clinical data relating to radioactive iodine use in children with GD and subsequent thyroid cancer (191), it is known that risks of thyroid cancer after external irradiation are highest in children <5 years of age, and they decline with advancing age (192,193); see discussion of ^{131}I therapy and cancer risk in [P3] below. In comparison, activities of radioactive iodine used with contemporary therapy are not known to be associated with an increased risk of thyroid neoplasm in children.

Thyroidectomy is an effective treatment for GD, but is associated with a higher complication rate in children than adults (194,195). Thyroidectomy should be performed in those children who are too young for radioactive iodine, provided that surgery can be performed by a high-volume thyroid surgeon, preferably with experience in conducting thyroidectomies in children.

Technical remarks: There may be circumstances in which ^{131}I therapy is indicated in very young children, such as when a child has developed a reaction to ATDs, proper surgical expertise is not available, or the patient is not a suitable surgical candidate.

[O] If antithyroid drugs are chosen as initial management of GD in children, how should the therapy be managed?

[O1] Initiation of antithyroid drug therapy for the treatment of GD in children

■ **RECOMMENDATION 51**

Methimazole should be used in virtually every child who is treated with antithyroid drug therapy. **1/++0**

Technical remarks: MMI comes in 5 or 10 mg tablets and can be given once daily, even in patients with severe hyperthyroidism. Although many practitioners give MMI in divided doses, data in adults do not support a need for such and show that compliance with once-daily MMI therapy is superior to multiple daily doses of PTU (83% vs. 53%) (196). The MMI dose typically used is 0.2–0.5 mg/kg daily, with a range from 0.1–1.0 mg/kg daily (197–204). One approach is to prescribe the following whole tablet or quarter to half-tablet doses: infants, 1.25 mg/day; 1–5 years, 2.5–5.0 mg/day; 5–10 years, 5–10 mg/day; and 10–18 years, 10–20 mg/day. With severe clinical or biochemical hyperthyroidism, doses that are 50%–100% higher than the above can be used.

When thyroid hormone levels normalize, MMI doses can be reduced by 50% or more to maintain a euthyroid state (205). Alternatively, some physicians elect not to reduce the MMI dose and add levothyroxine to make the patient euthyroid, a practice referred to as "block and replace." However, because meta-analyses suggest a higher prevalence of adverse events using block-and-replace regimens than dose titration (81,84,206), and there may be dose-related complications associated with MMI (207), we suggest that this practice in general be avoided.

■ **RECOMMENDATION 52**

Pediatric patients and their caretakers should be informed of side effects of antithyroid drugs and the necessity of stopping the medication immediately and informing their physician if they develop pruritic rash, jaundice, acolic stools or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, or pharyngitis. **1/+00**

■ **RECOMMENDATION 53**

Prior to initiating antithyroid drug therapy, we suggest that pediatric patients have, as a baseline, complete blood cell count, including white blood cell count with differential, and a liver profile including bilirubin, transaminases, and alkaline phosphatase. **2/+00**

PTU is associated with an unacceptable risk of hepatotoxicity in children, with a risk of liver failure of 1 in 2000–4000 children taking the medication (208–210). PTU can cause fulminant hepatic necrosis that may be fatal; liver transplantation has been necessary in some patients taking PTU (91). It is for this reason that the FDA recently issued a safety alert regarding the use of PTU, noting that 32 (22 adult and 10 pediatric) cases of serious liver injury have been associated with PTU use (92,93).

Because PTU-induced liver injury is of rapid onset and can be rapidly progressive, biochemical monitoring of liver function tests and transaminase levels is not expected to be useful in managing the hepatotoxicity risk in a PTU-treated patient (210). However, when neither prompt surgery nor ^{131}I therapy are options, and ATD therapy is necessary in a patient who has developed a minor toxic reaction to MMI, a short course of PTU use can be considered. When surgery is the planned therapy and MMI cannot be administered, if the patient is not too thyrotoxic (and the hyperthyroidism is due to GD), the hyperthyroid state can be controlled before surgery with beta blockade and SSKI (50 mg iodide/drop) 3–7 drops (0.15–0.35 mL) by mouth, given three times a day for 10 days before surgery).

Alternatively, if the surgery cannot be performed within a few weeks, a short course of PTU may be administered with the child closely monitored.

Technical remarks: It is advisable to provide information concerning side effects of ATDs to the patient in writing. This information can be found on the UpToDate Web site (99). See *Technical remarks* following Recommendation 15 for a discussion regarding the utility of obtaining complete blood count and liver profile before initiating methimazole therapy.

[O2] Symptomatic management of Graves' hyperthyroidism in children

■ **RECOMMENDATION 54**
Beta adrenergic blockade is recommended for children experiencing symptoms of hyperthyroidism, especially those with heart rates in excess of 100 beats per minute. **1/+00**

In children in whom the diagnosis of Graves' hyperthyroidism is strongly suspected or confirmed, and who are showing significant symptoms, including, but not limited to, tachycardia, muscle weakness, tremor, or neuropsychological changes, treatment with atenolol, propranolol, or metoprolol leads to a decrease in heart rate and symptoms of GD. In those with reactive airway disease, cardioselective beta-blockers can be used (211), with the patient monitored for exacerbation of asthma.

[O3] Monitoring of children taking methimazole

After initiation of MMI therapy, thyroid function tests (estimated free T_4, total T_3, TSH) are obtained monthly at first, and then every 2–4 months. Depending on the severity of hyperthyroidism, it can take several months for elevated thyroid hormone levels to fall into the normal range on ATDs.

■ **RECOMMENDATION 55**
Antithyroid medication should be stopped immediately, and white blood counts measured in children who develop fever, arthralgias, mouth sores, pharyngitis, or malaise. **1/+00**

Although MMI has a better overall safety profile than PTU, MMI is associated with minor adverse events that may affect up to 20% of children (212). MMI-related adverse events include allergic reactions, rashes, myalgias, and arthralgias (188,213,214), as well as hypothyroidism from overtreatment. Side effects to MMI usually occur within the first 6 months of starting therapy, but adverse events can occur later. In children, the risks of cholestasis and hepatocellular injury appear to be much less than that observed in adults.

Agranulocytosis has been reported in about 0.3% of adult patients taking MMI or PTU (81,207,215). Data on the prevalence of agranulocytosis in children are unavailable, but it is estimated to be very low. In adults, agranulocytosis is dose dependent with MMI, and rarely occurs at low doses (207,215). When agranulocytosis develops, 95% of the time it occurs in the first 100 days of therapy (207,215). The overall rate of side effects to ATDs (both major and minor) in children has been reported to be 6%–35% (214,216).

Technical remarks: While routine monitoring of white blood counts may occasionally detect early agranulocytosis, it is not recommended because of the rarity of the condition and its sudden onset, which is generally symptomatic. It is for this reason that measuring white cell counts during febrile illnesses and at the onset of pharyngitis has become the standard approach to monitoring.

[O4] Monitoring of children taking propylthiouracil

■ **RECOMMENDATION 56**
When propylthiouracil is used in children, the medication should be stopped immediately and liver function and hepatocellular integrity assessed in children who experience anorexia, pruritis, rash, jaundice, light-colored stool or dark urine, joint pain, right upper quadrant pain or abdominal bloating, nausea, or malaise. **1/+00**

Technical remarks: PTU should be discontinued if transaminase levels (obtained in symptomatic patients or found incidentally) reach 2–3 times the upper limit of normal and fail to improve within a week with repeat testing. After discontinuing the drug, liver function tests (i.e., bilirubin, alkaline phosphatase, and transaminases) should be monitored weekly until there is evidence of resolution. If there is no evidence of resolution, referral to a gastroenterologist or hepatologist is warranted.

[O5] Management of allergic reactions in children taking methimazole

■ **RECOMMENDATION 57**
Persistent minor cutaneous reactions to methimazole therapy in children should be managed by concurrent antihistamine treatment or cessation of the medication and changing to therapy with radioactive iodine or surgery. In the case of a serious allergic reaction to an antithyroid medication, prescribing the other antithyroid drug is not recommended. **1/+00**

If children develop serious allergic reactions to MMI, radioactive iodine or surgery should be considered because the risks of PTU are viewed to be greater than the risks of radioactive iodine or surgery. PTU may be considered for short-term therapy in this setting to control hyperthyroidism in preparation for surgery.

[O6] Duration of methimazole therapy in children with GD

■ **RECOMMENDATION 58**

If methimazole is chosen as the first-line treatment for GD in children, it should be administered for 1–2 years and then discontinued, or the dose reduced, to assess whether the patient is in remission. **1/++0**

The issue of how long ATDs should be used in children before considering either radioactive iodine or surgery is a topic of controversy and warrants further study. Prospective studies in adults show that if remission does not occur after 12–18 months of therapy, there is little chance of remission occurring with prolonged therapy (217). In children, when ATDs are used for 1–2 years, remission rates are generally 20%–30%, with remission defined as being euthyroid for 1 year after cessation of therapy (187,199,214,218,219). Retrospective studies have suggested that the chance of remission after 2 years of ATDs is low if the thyroid gland is large (more than 2.5 times normal size for age), the child is young (<12 years) (214,219) or not caucasian, serum TRAb levels are above normal on therapy, or FT4 estimates are substantially elevated at diagnosis (>4 ng/dL; 50 pmol/L) (214). One prospective study suggested that likelihood of remission could best be predicted by the initial response to antithyroid medication, with achievement of euthyroid state within 3 months, suggesting higher likelihood. Younger children and those with high initial thyroid hormone levels were also found to be less likely to achieve remission within 2 years in the prospective study (214).

Remission rates in children treated with ATDs for longer than 2 years have been reported. Although two decades ago it was suggested that 25% of children with GD go into remission with every 2 years of continued treatment (220), other studies of larger cohorts of pediatric patients with GD treated with ATDs for extended periods have not revealed similar remission rates (213,216,221). Of 120 pediatric patients treated with ATDs at one center, after 1 year of therapy with ATDs, 25% were in remission; after 2 years, 26%; after 4 years, 37%; and after 4–10 years, 15%. Importantly, 30% of the children who went into remission eventually relapsed (213). In another large cohort of 184 medically treated children, after 1 year of therapy with ATDs, 10% were in remission; after 2 years, 14%; after 3 years, 20%; and after 4 years, 23% (221).

Data also suggest that there are age-related differences in responsiveness to ATDs. In one study that compared outcomes of 32 prepubertal and 68 pubertal children, remission occurred in only 17% of prepubertal children treated 5.9 ± 2.8 years, compared with 30% of pubertal individuals treated 2.8 ± 1.1 years (219). In another report, the course of GD was compared in 7 prepubertal, 21 pubertal, and 12 postpubertal children (216). Remission was achieved in 10 patients (28%) with similar rates among the three groups, whereas the time to remission tended to be longer in the small proportion of prepubertal children (median age, 6 years) (216).

Persistence of GD in children is correlated with the persistence of TRAbs. A recent study found that TRAb levels normalized after 24 months in only 18% of pediatric patients on ATDs (204). There were no data showing that there was normalization of TRAb levels when patients were on ATDs for a longer time. Therefore, it appears that TRAb levels persist longer in children than in adults (204). Whereas monitoring of TRAb levels while on ATDs has been shown to be useful in adult patients for predicting the likelihood of remission or relapse of GD after stopping the medication (222), this approach has yet to be validated in children.

■ **RECOMMENDATION 59**

Pediatric patients with GD who are not in remission following 1–2 years of methimazole therapy should be considered for treatment with radioactive iodine or thyroidectomy. **1/+00**

If after stopping MMI after 1 or 2 years' remission is not achieved, ^{131}I or surgery should be considered, depending on the age of the child. Alternatively, practitioners can continue MMI for extended periods, as long as adverse drug effects do not occur and the hyperthyroid state is controlled. This approach can be used as a bridge to ^{131}I therapy or surgery at a later age if remission does not occur. In selected situations where it might not be suitable or possible to proceed with ^{131}I or surgery, low-dose MMI can be continued, although the likelihood of remission is not great.

[P] If radioactive iodine is chosen as treatment for GD in children, how should it be accomplished?

[P1] Preparation of pediatric patients with GD for ^{131}I therapy

■ **RECOMMENDATION 60**

We suggest that children with GD having total T_4 levels of >20 ug/dL (260 nmol/L) or free T_4 estimates >5 ng/dL (60 pmol/L) who are to receive radioactive iodine therapy be pretreated with methimazole and beta-adrenergic blockade until total T_4 and/or free T_4 estimates normalize before proceeding with radioactive iodine. **2/+00**

Although the frequency of short-term worsening of hyperthyroidism following pretreatment with ATD therapy is not known, there are rare reports of pediatric patients with severe hyperthyroidism who have developed thyroid storm after receiving ^{131}I (223).

Technical remarks: When children receiving MMI are to be treated with ^{131}I, the medication is stopped 3–5 days before treatment (224). At that time, patients are placed on beta-blockers, which they continue to take until total T_4 and/or free T_4 estimate levels normalize following radioactive iodine therapy. Although some physicians restart ATDs after treatment with ^{131}I (225), this practice is seldom required in children (188,189,224,226). Thyroid hormone levels in children begin to fall within the first week following radioactive iodine therapy. ATDs can complicate assessment of post-treatment hypothyroidism, since it could be the result of the MMI rather than the ^{131}I therapy.

[P2] Administration of ^{131}I in the treatment of GD in children

■ **RECOMMENDATION 61**

If ^{131}I therapy is chosen as treatment for GD in children, sufficient ^{131}I should be administered in a single dose to render the patient hypothyroid. **1/++0**

The goal of ^{131}I therapy for GD is to induce hypothyroidism, rather than euthyroidism, as lower administered activities of ^{131}I result in residual, partially irradiated thyroid tissue that is at increased risk for thyroid neoplasm development (69,227). Because of an increased risk of thyroid nodules and cancer associated with low-level thyroid irradiation in children (192–194,228,229), and poor remission rates with low-administered activities of ^{131}I (61,64,65,188), it is important that larger (>150 μCi of ^{131}I per gram of thyroid tissue) rather than smaller activities of ^{131}I be administered to achieve hypothyroidism (230). With large glands (50–80 g), higher administered activities of ^{131}I (200–300 μCi of ^{131}I per gram) may be needed (224). The administered activity of ^{131}I to patients with very large goiters is high, and there is a tendency to underestimate the size of the gland (and thereby administer insufficient radiation to these patients) (64). Therefore, surgery in patients with goiters larger than 80 g may be preferable to radioactive iodine therapy.

Physicians at some centers administer a fixed dose of about 15 mCi ^{131}I to all children (226), whereas others calculate the activity from estimation or direct measurement of gland size and ^{123}I uptake (224). To assess thyroid size, particularly in the setting of a large gland, ultrasonograhy is recommended (231). There are no data comparing outcomes of fixed versus calculated activities in children; in adults, similar outcomes have been reported with the two approaches (232). One potential advantage of calculated versus fixed dosing is that it may be possible to use lower administered activities of ^{131}I, especially when uptake is high and the thyroid is small. Calculated dosing also will help assure that an adequate administered activity is given. When activities >150 μCi of ^{131}I per gram of thyroid tissue are administered, hypothyroidism rates are about 95% (188,233,234). While there are reports that hyperthyroidism can relapse in pediatric patients rendered hypothyroid with ^{131}I, this is very infrequent.

Technical remarks: Radioactive iodine is excreted by saliva, urine, and stool. Significant radioactivity is retained within the thyroid for several days. It is therefore important that patients and families be informed of and adhere to local radiation safety recommendations following ^{131}I therapy. After ^{131}I therapy, T_3, T_4, and/or estimated free T_4 levels should be obtained every month. Because TSH levels may remain suppressed for several months after correction of the hyperthyroid state, TSH determinations may not be useful in this setting for assessing hypothyroidism. Hypothyroidism typically develops by 2–3 months post-treatment (224,226), at which time levothyroxine should be prescribed.

[P3] Side-effects of ^{131}I therapy in children

Side effects of ^{131}I therapy in children are uncommon apart from the lifelong hypothyroidism that is the goal of therapy. Less than 10% of children complain of mild tenderness over the thyroid in the first week after therapy; it can be treated effectively with acetaminophen or nonsteroidal anti-inflammatory agents for 24–48 hours (189,224). If there is residual thyroid tissue in young children after radioactive iodine treatment, there is a theoretical risk of development of thyroid cancer. Detractors of the use of ^{131}I therapy in children point to the increased rates of thyroid cancer and thyroid nodules observed in young children exposed to radiation from nuclear fallout at Hiroshima or after the Chernobyl nuclear reactor explosion. However, these data do not apply directly when assessing risks of ^{131}I therapy. The risk of thyroid neoplasia is greatest with exposure to low level external radiation (0.1–25 Gy; ~0.09–30 μCi/g) (192,193,228,235,236), not with the higher administered activities used to treat GD. It is also important to note that iodine deficiency and exposure to radionuclides other than ^{131}I may have contributed to the increased risk of thyroid cancer in young children after the Chernobyl reactor explosion (192). Notably, thyroid cancer rates were not increased among 3000 children exposed to ^{131}I from the Hanford nuclear reactor site in an iodine-replete region (237). Increased thyroid cancer rates also were not seen in 6000 children who received ^{131}I for the purpose of diagnostic scanning (238).

There is no evidence to suggest that children or adults treated for GD with more than 150 μCi of ^{131}I per gram

of thyroid tissue have an increased risk of thyroid cancer directly attributable to the radioactive iodine. While there are several studies of this issue in adults treated with radioactive iodine for GD (see section D2), few studies have focused on populations exposed to ^{131}I for the treatment of GD in childhood or adolescence.

In one study, an analysis was carried out of 602 individuals exposed to ^{131}I below 20 years of age in Swedish and U.S. populations (239). The average follow-up period was 10 years, and the mean administered activity of radioactive iodine to the thyroid was 88 Gy (approximately 80 μCi/g equivalent), an activity known to be associated with thyroid neoplasia and below that recommended for treatment of GD. Two cases of thyroid cancer were reported compared to 0.1 cases expected over that period of time. Effects on the development of nonthyroid cancers were not examined.

The pediatric study with the longest follow-up reported 36-year outcomes of 116 patients, treated with ^{131}I between 1953 and 1973 (240). The patients ranged in age at treatment from 3 to 19 years. No patient developed thyroid cancer or leukemia. There was no increase in the rate of spontaneous abortion or in the number of congenital anomalies in offspring. It is important to note that sample size was small; thus, the statistical power was inadequate to address this issue fully.

Total body radiation dose after ^{131}I varies with age, and the same absolute activities of ^{131}I will result in more radiation exposure to a young child than to an adolescent or adult (241). At present, we do not have dosimetry information regarding ^{131}I use in children with GD to assess total body exposure in children. Using phantom modeling, it has been estimated that at 0, 1, 5, 10, and 15 years of age, and adulthood, respective total body radiation activities are 11.1, 4.6, 2.4, 1.45, 0.90, and 0.85 rem (1 rem = 0.1 Sv) per mCi of ^{131}I administered (241). Based on the Biological Effects of Ionizing Radiation Committee VII analysis of acute, low-level radiation exposure (242), the theoretical lifetime attributable risk of all-cancer incidence and all-cancer mortality for a large population of treated children can be estimated (Table 7).

To date, long-term studies of children treated with ^{131}I for GD have not revealed an increased risk of nonthyroid malignancies (239). If a small risk exists, a sample size of more than 10,000 children who were treated at <10 years of age would be needed to identify the risk, likely exceeding the number of such treated children. Based on cancer risk projections from estimated whole-body, low-level radiation exposure as related to age, it is theoretically possible that there may be a low risk of malignancies in very young children treated with ^{131}I. Thus, we recommended above that radioactive iodine therapy be avoided in very young children (<5 years) and that radioactive iodine be considered in those children between 5 and 10 years of age when the required activity for treatment is <10 mCi. It is important to emphasize that these recommendations are based on theoretical concerns and further direct study of this issue is needed. The theoretical risks of ^{131}I use must therefore be weighed against the known risks inherent in thyroidectomy or prolonged ATD use when choosing among the three different treatment options for GD in the pediatric age group.

The activity of radioactive iodine administered should be based on thyroid size and uptake, and not arbitrarily reduced because of age in young individuals. Attempts to minimize the radioactive iodine activity will result in undertreatment and the possible need for additional radioactive iodine therapy and radiation exposure.

Table 7. Theoretical Projections of Cancer Incidence or Cancer Mortality Related to ^{131}I Therapy for Hyperthyroidism as Related to Age

Age at exposure (year)	*Total-body ^{131}i dose (rem or rad)*		*Lifetime attributable risk of cancer mortality per 100,000 per 0.1 Gy or SV per 100,000 per rad or rem*						*Lifetime cancer risk for 15 mCi ^{131}I*		*Relative lifetime cancer risk for 15 mCi ^{131}I*[a]
	Per mCi	*Per 15 mCi*	*Males*	*Female*	*Average*	*Males*	*Female*	*Average*	*Cases per 100,000*	*%*	
0	11.1	167	1099	1770	1435	110	177	143	23,884	23.9	1.96
1	4.6	69.0	1099	1770	1435	110	177	143	9898	9.9	1.40
5	2.4	36.0	852	1347	1100	85	135	110	3958	3.96	1.16
10	1.45	21.8	712	1104	908	71	110	91	1975	1.97	1.08
15	0.9	13.5	603	914	759	60	91	76	1024	1.02	1.04
20	0.85	12.8	511	762	637	51	76	64	812	0.81	1.03
40	0.85	12.8	377	507	442	38	51	44	564	0.56	1.02
60	0.85	12.8	319	409	364	32	41	36	464	0.46	1.02

[a]Using a gross average of dying from a spontaneous cancer of 25% data analysis by Dr. Patrick Zanzonico, Memorial Sloan Kettering Cancer Center (New York, NY).

Q] If thyroidectomy is chosen as treatment for GD in children, how should it be accomplished?

[Q1] Preparation of children with GD for thyroidectomy

■ **RECOMMENDATION 62**
Children with GD undergoing thyroidectomy should be rendered euthyroid with the use of methimazole. Potassium iodide should be given in the immediate preoperative period. **1/+00**

Surgery is an acceptable form of therapy for GD in children. Thyroidectomy is the preferred treatment for GD in young children (<5 years) when definitive therapy is required, and the surgery can be performed by a high-volume thyroid surgeon. In individuals with large thyroid glands (>80 g), the response to ^{131}I may be poor (64,65); surgery also may be preferable for these patients. When performed, near-total or total thyroidectomy is the recommended procedure (243).

Technical remarks: MMI is typically given for 1–2 months in preparation for thyroidectomy. Ten days before surgery, potassium iodide (SSKI; 50 mg iodide/drop) can be given as 3–7 drops (i.e., 0.15–0.35 mL) three times daily for 10 days before surgery.

■ **RECOMMENDATION 63**
If surgery is chosen as therapy for GD in children, total or near-total thyroidectomy should be performed. **1/++0**

■ **RECOMMENDATION 64**
Thyroidectomy in children should be performed by high-volume thyroid surgeons. **1/++0**

Surgical complication rates are higher in children than in adults, with higher rates in younger than in older children (194). Postoperatively, younger children also appear to be at higher risk for transient hypoparathyroidism than adolescents or adults (194).

In addition, complication rates are twofold higher when thyroidectomy is performed by pediatric or general surgeons who do not have extensive current experience in this procedure than when performed by high-volume thyroid surgeons (194). Further support for the notion that thyroidectomy for GD in children should be performed by experienced thyroid surgeons comes from reports of institutional experience showing low complication rates at high-volume centers (190,244). In circumstances where local pediatric thyroid surgery expertise is not available, referral of a child with GD to a high-volume thyroid surgery center that also has pediatric experience is indicated, especially for young children. A multidisciplinary health-care team that includes pediatric endocrinologists and experienced thyroid surgeons and anesthesiologists is optimal.

[R] How should SH be managed?

[R1] Frequency and causes of SH

SH has a prevalence of about 1% in the general population (245). In older persons, TMNG is probably the most common cause of SH, with other etiologies of endogenous SH, including GD, solitary autonomously functioning nodules, and various forms of thyroiditis (246,247), the latter of which would be more strictly termed "subclinical thyrotoxicosis." Some otherwise healthy older persons may have low serum TSH levels, low normal serum levels of free T_4 estimates and T_3, and no evidence of thyroid or pituitary disease, suggesting an altered set point of the pituitary-thyroid axis (248,249). This situation can mimic SH biochemically, and it may be difficult to rule out clinically, although scintigraphic studies suggesting autonomous thyroid function would favor SH. Other causes of a suppressed TSH but normal estimated free T_4 and T_3 include corticosteroid therapy, central hypothyroidism, and nonthyroidal illness. Once SH has been detected, it is important to document that it is a persistent problem by repeating the serum TSH at 3 or 6 months. Some reports suggest that a subnormal serum TSH may spontaneously resolve, especially if the levels are >0.05 mU/L (250–252). Patients with GD rather than a TMNG as the cause of SH may be more likely to spontaneously remit (253).

[R2] Clinical significance of SH

Since SH is a mild form of hyperthyroidism, deleterious effects on the cardiovascular system and the skeleton might be expected in some patients, and subtle symptoms of thyrotoxicosis or altered cognition might also be potential problems. Regarding cardiac complications, one study found a 2.8-fold risk of atrial fibrillation in persons over age 60 years with SH (254), which has been confirmed in another population over age 65 years (255). Small uncontrolled studies have shown improvement in cardiac parameters, with restoration of a euthyroid state (256,257) or the use of beta adrenergic blocking drugs (258).

Postmenopausal women with SH may have increased fracture rates even with only mildly suppressed serum TSH levels (259), as well as improvement in bone mineral density with therapy of SH with antithyroid drugs or radioactive iodine in controlled but nonrandomized intervention studies (260,261). There are also preliminary data suggesting an increase in bone turnover (262) and lower bone density in premenopausal women with SH (263). Another uncontrolled study has shown an increase in muscle mass and muscle strength in middle-aged women with SH after

treatment with radioactive iodine or thyroidectomy (264). For patients receiving levothyroxine replacement therapy, only those with a suppressed TSH had an increased risk of cardiac or bone disease, whereas those with a low, but unsuppressed level did not (265).

One cross-sectional (266) and one longitudinal (267) study of older individuals showed no changes in cognitive function, whereas two others suggested an association between SH and dementia in older persons (268,269). Finally, there is the potential risk of progression to overt hyperthyroidism if SH is left untreated. This risk is probably somewhere between 0.5% and 1% per year (270,271). Data on the effects of SH on mortality are conflicting. In one study, all-cause and cardiovascular mortality were higher in a group of individuals with SH (serum TSH <0.5 mU/L) aged 60 years and older at 1, 2, and 5 years of follow-up, but not after 10 years of follow-up (271). Another study also found an increase in mortality over 4 years of follow-up among persons aged 85 years and above (267), in a third study, individuals with SH and concomitant heart disease had an increase in cardiovascular and all-cause mortality (272). In contrast, two other longitudinal population-based studies reported no increase in overall mortality in persons with SH (255,273). A recent meta-analysis suggested that all-cause mortality risk in SH progressively increases with age (274), which might explain the conflicting reports. Another meta-analysis, however, did not find a statistically significant increase in mortality in SH (275).

[R3] When to treat SH

■ **RECOMMENDATION 65**

When TSH is persistently <0.1 mU/L, treatment of SH should be strongly considered in all individuals ≥65 years of age, and in postmenopausal women who are not on estrogens or bisphosphonates; patients with cardiac risk factors, heart disease or osteoporosis; and individuals with hyperthyroid symptoms**. 2/+**+0

Treatment of SH is controversial, since no controlled intervention studies to show benefit have been performed. However, a panel of experts determined that the evidence for benefit was sufficient to warrant therapy of SH in older individuals whose serum TSH level was <0.1 mU/L (276). This was based primarily on the studies showing an increased rate of atrial fibrillation and altered skeletal health with a suppressed level of TSH described above.

There are insufficient data for or against treatment of SH in younger persons or premenopausal women with SH and serum TSH <0.1 mU/L. One uncontrolled study of middle-aged patients showed an improvement in hyperthyroid symptoms with therapy (256). Although this study did not include younger individuals, the task force elected to recommend treatment of all SH patients younger than 65 years of age with persistent TSH <0.1 mU/L and hyperthyroid symptoms.

Technical remarks: A TSH level of <0.1 mU/L on repeated measurement over a 3–6-month period is considered to be persistent, effectively ruling out transient thyroiditis as a cause. The thyroid disorder underlying SH should be diagnosed, and is most commonly TMNG, GD, or TA.

■ **RECOMMENDATION 66**

When TSH is persistently below the lower limit of normal but ≥0.1 mU/L, treatment of SH should be considered in individuals ≥65 years of age and in patients with cardiac disease or symptoms of hyperthyroidism. **2/+00**

Since the publication of the expert panel report discussed above, a subsequent study showed that a higher risk of atrial fibrillation may extend to persons over age 65 years who have serum TSH levels between 0.1 and 0.5 mU/L (where 0.5 mU/L is the lower limit of the normal range for the assay) (255). Therefore, justification for therapy in patients with this higher TSH threshold level rests with those data, as well as a meta-analysis showing a progressive increase in mortality in individuals older than 60 years of age (274). In contrast, an observational cohort study of T_4-treated patients could find no such relationship with TSH levels between 0.04 and 0.4 mU/L. There are no data for or against treatment of individuals younger than middle-aged with serum TSH levels between 0.1 and 0.5 mU/L. In patients with symptoms of hyperthyroidism, a trial of beta-adrenergic blockers may be useful to determine whether symptomatic therapy might suffice.

Technical remarks: A TSH level between 0.1 and 0.5 mU/L on repeated measurement over a 3–6-month period is considered persistent, effectively ruling out transient thyroiditis as a cause. The thyroid disorder underlying SH with TSH persistently within this range should be diagnosed to avoid treating patients with transient, functional disorders related to acute illness, drugs, and other causes of low TSH. A summary of factors to consider when deciding whether or not to treat a patient with SH is provided (Table 8).

[R4] How to treat SH

■ **RECOMMENDATION 67**

If SH is to be treated, the treatment should be based on the etiology of the thyroid dysfunction and follow the same principles as outlined for the treatment of overt hyperthyroidism. **1/+00**

Table 8. Subclinical Hyperthyroidism: When to Treat

Factor	*TSH (<0.1 mU/L)*	*TSH (0.1–0.5 mU/L)*[a]
Age >65	Yes	Consider treating
Age <65 with comorbidities		
Heart disease	Yes	Consider treating
Osteoporosis	Yes	No
Menopausal	Consider treating	Consider treating
Hyperthyroid symptoms	Yes	Consider treating
Age <65, asymptomatic	Consider treating	No

[a]Where 0.5 mU/L is the lower limit of the normal range.

The treatment of SH is similar to the treatment of overt hyperthyroidism. Radioactive iodine is appropriate for most patients, especially in older patients when TMNG is a frequent cause of SH. There are no data to inform whether elderly patients with SH would benefit from pretreatment with ATDs to normalize thyroid function before radioactive iodine therapy. Given the low risk of exacerbation (51), the risks of ATD therapy may outweigh any potential small benefit. Long-term ATD therapy is a reasonable alternative to radioactive iodine in patients with GD and SH, especially in younger patients, since remission rates are highest in persons with mild disease (81). Some patients with SH due to GD may remit spontaneously without therapy, so that continued observation without therapy is reasonable for younger patients with SH due to GD. A small subset of elderly patients with persistently low TSH and no evidence of true thyroid dysfunction can be followed without intervention, especially when the serum FT_4 estimate and T_3 levels are in the lower half of the normal range. Treatment with beta-adrenergic blockade may be sufficient to control the cardiovascular-related morbidity from SH, especially that of atrial fibrillation (258).

Technical remarks: Some patients with SH due to mild GD may remit spontaneously and may be followed without therapy with frequent (every 3 months) monitoring of thyroid function. In select patients with SH due to TMNG who have compressive symptoms, or in whom there is concern for malignancy, surgery is also an option.

[R5] End points to be assessed to determine effective therapy of SH

The goal of therapy for SH is to render the patient euthyroid with a normal TSH. Since the rationale for therapy of SH is to a large degree preventive, there are few end points that can be used to document that therapy has been successful. There are no studies to show that therapy prevents the onset of atrial fibrillation or decreases mortality. Several studies have shown stabilization or improvement in bone mineral density with therapy of SH in postmenopausal women (260,261,277). One uncontrolled study reported an improvement in hyperthyroid symptoms with antithyroid drug therapy of SH (256) and a second report showed improvement in the hyperthyroid symptoms of SH after treatment with beta-adrenergic blockade (258).

[S] How should hyperthyroidism in pregnancy be managed?

Hyperthyroidism due to GD is common in women in the reproductive age range and both the thyrotoxicosis and therapy of the disease may complicate the course and outcome of pregnancy. Further, normal pregnancy is accompanied by changes in thyroid physiology, and altered thyroid function testing will reflect this. In early pregnancy, physiological changes can mimic biochemical hyperthyroidism that does not require therapy. In these guidelines, we will address only the most common issues related to hyperthyroidism in pregnancy, pending full guidelines on thyroid disease and pregnancy currently being developed by the ATA.

[S1] Diagnosis of hyperthyroidism in pregnancy

■ **RECOMMENDATION 68**

The diagnosis of hyperthyroidism in pregnancy should be made using serum TSH values, and either total T_4 and T_3 with total T_4 and T_3 reference range adjusted at 1.5 times the nonpregnant range or free T_4 and free T_3 estimations with trimester-specific normal reference ranges. **1/+00**

The diagnosis of hyperthyroidism in pregnancy can be challenging. In the vast majority of patients, the disease is caused by a primary thyroid abnormality, and the principal finding will be a suppressed serum TSH, with estimated serum free T_4 and/or free T_3 levels above the reference

range (overt hyperthyroidism), or within the reference range (SH). A key point is that reference ranges for thyroid function tests are different during various stages of pregnancy, and for some types of assays, the change may be assay-dependent. GD is the most common cause of hyperthyroidism during pregnancy (278); nodular thyroid disease is less common. Hyperthyroidism caused by a human chorionic gonadotropin (hCG)-producing molar pregnancy or a choriocarcinoma presents with a diffuse hyperactive thyroid similar to GD, but without eye signs and without serum TRAb. In these patients, serum hCG will be higher than expected, and the cause can be identified by obstetrical investigation.

An understanding of pregnancy-related variations in thyroid function tests is important in making the diagnosis of hyperthyroidism in pregnancy. Serum TSH levels may be below the nonpregnant reference range in the first half of a normal-term pregnancy (279,280), presumably the result of stimulation of the normal thyroid by high levels of serum hCG (281). Therefore, low serum TSH levels with normal free T_4 values in early pregnancy do not indicate abnormal thyroid function. During the second half of pregnancy, the lower limit for TSH in the nonpregnant population can be used (282).

Free T_4 and T_3 measured in an equilibrium dialysate or an ultrafiltrate of serum may be slightly higher (5%–10%) than nonpregnancy values around week 10 of pregnancy, corresponding to the period of high serum hCG and low serum TSH. From this normal or slightly high level, a gradual decrease occurs during pregnancy, and late third trimester reference values are 10%–30% below nonpregnancy values (283).

Serum total T_4 and T_3 increase in early pregnancy. From the late first trimester, they remain stable, with reference ranges close to 1.5 times nonpregnancy ranges during the second and third trimesters (283,284). Total T_4 and T_3 values may be combined with a T_3 uptake test or measurements of TBG to adjust for pregnancy-associated variations in TBG. Such "free T_4 index" or "TBG adjusted T_4" values may be useful for diagnosing hyperthyroidism in pregnancy. However, trimester-specific normal reference ranges should be established for each individual test and assay used.

Technical remarks: The reliability of automated analog-based assays for free T_4 and free T_3 estimations has been questioned for more than 25 years (285), but these estimates are currently widely used; in many clinics, they are the standard of measurement in pregnancy. Because pregnancy may influence results of these assays from different manufacturers in different ways (286), method-specific reference ranges for each trimester of pregnancy should be employed by the manufacturer (287,288).

[S2] Management of hyperthyroidism in pregnancy

■ **RECOMMENDATION 69**

Transient hCG-mediated thyrotropin suppression in early pregnancy should not be treated with antithyroid drug therapy. **1/+00**

Once the diagnosis of hyperthyroidism is made in a pregnant woman, attention should be focused on determining the etiology of the disorder and whether it warrants treatment. Clinical features that may indicate the presence of significant hyperthyroidism include failure to gain weight, heat intolerance, excessive sweating, and tachycardia, beyond that normally associated with pregnancy.

The two most common types of biochemical hyperthyroidism that occur during pregnancy are gestational hyperthyroidism (e.g., hCG-mediated transient TSH suppression) and GD. Gestational hyperthyroidism is a generally asymptomatic, mild biochemical hyperthyroidism that may be observed in the first trimester of normal pregnancy. It is presumably caused by the high serum hCG of early pregnancy (281) and is not associated with adverse pregnancy outcomes (289). Pregnant women having gestational hyperthyroidism with emesis, and particularly hyperemesis, may develop more profound abnormalities in thyroid function, with biochemically overt hyperthyroidism and clinical symptoms and signs of hyperthyroidism. Complicated cases of gestational hyperthyroidism should be referred to medical centers with specific expertise in treating these patients.

Technical remarks: There is no evidence that treatment of gestational hyperthyroidism with ATDs is beneficial. In these patients, physical examination and repeat thyroid function tests at intervals of 3–4 weeks is recommended. If the differential diagnosis of the type of hyperthyroidism is unclear (i.e., if there is suspicion of GD) or in the case of very symptomatic disease, a trial of ATD therapy may be considered if significant clinical hyperthyroidism is evident.

■ **RECOMMENDATION 70**

Antithyroid drug therapy should be used for hyperthyroidism due to GD that requires treatment during pregnancy. Propylthiouracil should be used when antithyroid drug therapy is started during the first trimester. Methimazole should be used when antithyroid drug therapy is started after the first trimester. **1/+00**

Untreated or insufficiently treated hyperthyroidism may seriously complicate pregnancy (290–292), and patients with this disorder should be treated at centers with specific expertise in this area. GD as the cause of

hyperthyroidism in pregnancy may be diagnosed from typical clinical findings, including the presence of GO and/or serum TRAb in a hyperthyroid patient. Approximately 5% of patients with newly diagnosed Graves' hyperthyroidism are TRAb negative (43,293), especially those with milder disease.

A woman found to have GD before pregnancy and treated with ATD who goes into remission and is euthyroid off medication has a low risk of recurrent hyperthyroidism during pregnancy. However, her risk of relapse (as well as the risk of postpartum thyroiditis) during the postpartum period is relatively high (294). Antithyroid drugs have much the same effect on thyroid function in pregnant as in nonpregnant women. Both ATDs and TRAb pass the placenta and can affect fetal thyroid. On the other hand, T_4 and T_3 cross the placenta only in limited amounts.

PTU generally has been preferred in pregnancy because of concerns about rare but well-documented teratogenicity associated with MMI, namely, aplasia cutis and choanal or esophageal atresia (81). However, recent concerns about rare but potentially fatal PTU hepatotoxicity have led to a re-examination of the role of PTU in the management of hyperthyroidism in pregnancy (92). The U.S. Food and Drug Administration recently recommended that PTU be reserved for patients who are in their first trimester of pregnancy, or who are allergic to or intolerant of MMI (92,93).

MMI and PTU both appear in breast milk in small concentrations and studies of breast-fed infants of mothers taking ATDs have demonstrated normal thyroid function and subsequent intellectual development (81). However, because of the potential for hepatic necrosis in either mother or child from maternal PTU use, MMI is the preferred ATD in nursing mothers.

■ **RECOMMENDATION 71**

We suggest that patients taking methimazole who decide to become pregnant obtain pregnancy testing at the earliest suggestion of pregnancy and be switched to propylthiouracil as soon as possible in the first trimester and changed back to methimazole at the beginning of the second trimester. Similarly, we suggest that patients started on propylthiouracil during the first trimester be switched to methimazole at the beginning of the second trimester. **2/+00**

Concern is that changing back and forth between MMI and PTU might lead to poorly controlled thyroid function because of differences in pharmacokinetics and uncertainty about dose equivalency between the two drugs. This situation is complicated by the changing levels of TRAb in pregnancy. In general, a potency ratio of MMI to PTU of at least 20–30:1 is recommended when changing from one drug to another, although there are no studies that have examined this potency ratio directly. For example, 300 mg of PTU would be roughly equivalent to 10 to15 mg of MMI (81). Alternatively, rather than switching to MMI at the end of the first trimester, the patient could remain on PTU during the second and third trimesters, and have hepatic enzymes measured every 4 weeks, at the same time that thyroid function is assessed. However, there are no prospective data that show that this type of monitoring is effective in preventing fulminant PTU-related hepatotoxicity.

■ **RECOMMENDATION 72**

GD during pregnancy should be treated with the lowest possible dose of antithyroid drugs needed to keep the mother's thyroid hormone levels slightly above the normal range for total T_4 and T_3 values in pregnancy and the TSH suppressed. Free T_4 estimates should be kept at or slightly above the upper limit of the nonpregnant reference range. Thyroid function should be assessed monthly, and the antithyroid drug dose adjusted as required. **1/+00**

Even if the mother is euthyroid during ATD therapy, there is a risk of inducing fetal hypothyroidism during the second and third trimesters when the fetal thyroid has begun to function (295,296). Thus, the dose of ATD should be kept as low as possible. Block-replacement therapy consisting of ATD plus levothyroxine should not be used in pregnancy. If a woman receiving such therapy becomes pregnant, therapy should be changed to an ATD alone (278).

Technical remarks: Free T_4 is the parameter that has been most closely correlated with good fetal outcome. Serum TSH may still be suppressed in these patients and should not be used as the sole guide in treatment, although normalization of maternal TSH during ATD therapy may indicate a need to reduce the dose of ATD (278).

■ **RECOMMENDATION 73**

When thyroidectomy is necessary for the treatment of hyperthyroidism during pregnancy, the surgery should be performed if possible during the second trimester. **1/+00**

Pregnancy is a relative contraindication to thyroidectomy and should only be used in this circumstance when aggressive medical management has not obviated the need for immediate treatment of the hyperthyroidism and antithyroid medications cannot be used. Thyroidectomy is best avoided in the first and third trimesters of pregnancy because of teratogenic effects associated with anesthetic agents and increased risk of fetal loss in the first trimester and increased risk of preterm labor in the third. Optimally, thyroidectomy would be performed in the latter portion of

the second trimester. Although it is the safest time, it is not without risk (4.5%–5.5% risk of preterm labor) (47,48). Evaluation by a high-risk obstetrician is advised along with counseling before surgery regarding risks involved (48). Thyroidectomy cures the hyperthyroid condition and is often followed by a gradual reduction in TRAb from the circulation (297). Until such remission takes place, TRAb produced by the mother may stimulate the thyroid of the fetus or newborn and induce hyperthyroidism. In the setting where the mother still harbours high levels of TRAb after thyroidectomy, close fetal monitoring for both cardiovascular and skeletal changes (fetal ultrasound) must be established.

There are no data concerning whether SSKI or iodine should be used to prepare pregnant patients for thyroidectomy. The risk of iodide therapy to the fetus is inhibition of iodine organification, the Wolff-Chaikoff effect. The fetal thyroid gland is particularly susceptible to the inhibitory effects of excess iodine at the end of gestation, and fetal goiter can occur with chronic therapy (298). However, there is no evidence that brief iodine preparation of the mother done preoperatively to reduce thyroid blood flow and control hyperthyroidism is harmful to the fetus.

Technical remarks: Preoperative preparation for thyroidectomy during the second trimester of pregnancy includes 10–14 days of iodine, along with ATD therapy and beta-blockers to control hyperthyroidism (299–301).

[S3] The role of TRAb levels measurement in pregnancy

■ **RECOMMENDATION 74**
TRAb levels should be measured when the etiology of hyperthyroidism in pregnancy is uncertain. **1/+00**

The two best indicators of the activity of GD during pregnancy are thyroid function in the untreated patient and measurement of TRAb levels in the serum. TRAb measurement is useful in the diagnosis of GD in pregnant women with newly diagnosed hyperthyroidism who do not have clinical signs specific for GD, keeping in mind that the diagnostic sensitivity of good assays is around 95%, and the specificity is 99% (43).

■ **RECOMMENDATION 75**
Patients who were treated with radioactive iodine or thyroidectomy for GD prior to pregnancy should have TRAb levels measured using a sensitive assay either initially at 22–26 weeks of gestation, or initially during the first trimester and, if elevated, again at 22–26 weeks of gestation. **1/+00**

Measurement of TRAb levels can detect persistent TSH-receptor autoimmunity in a pregnant woman previously treated with ablative therapy (radioactive iodine or thyroidectomy) for GD who is now euthyroid with or without thyroid hormone replacement (297,302). If the mother still produces TRAb, they will cross the placenta and may affect fetal thyroid function in the last half of the pregnancy. Because of the slow clearance of maternal immunoglobulin G (IgG) from the neonatal circulation, thyroid dysfunction in the child may last for several months after birth. To evaluate the risk of such complications, a TRAb level should be measured in the pregnant woman either initially at 22–26 weeks of gestation, or initially during the first trimester and, if elevated, again at 22–24 weeks of gestation. If the level is high, a program of fetal and neonatal surveillance for thyroid dysfunction should be initiated (303). While measuring TRAb levels only at 22–26 weeks is more cost effective, the advantage to initial measurement during the first trimester is that this allows more time to initiate specialty consultation and, if the levels are found to be especially high at that time, intervention may be required before the third trimester. TRAb measurement is not necessary in a euthyroid pregnant patient previously found to have GD if she has an intact thyroid (i.e., not previously treated with surgery or radioactive iodine) and is not currently taking ATDs (295,297).

■ **RECOMMENDATION 76**
Patients found to have GD during pregnancy should have TRAb levels measured at diagnosis using a sensitive assay and, if elevated, again at 22–26 weeks of gestation. **1/+00**

■ **RECOMMENDATION 77**
TRAb levels measured at 22–26 weeks of gestation should be used to guide decisions regarding neonatal monitoring. **1/+00**

TRAb (TBII or TSI) measurement is also useful to assist in the evaluation of disease activity in a woman being treated with ATDs for GD during pregnancy (297). In many patients, GD gradually remits during pregnancy. Disappearance of TRAb is an indication that ATD therapy may no longer be necessary, and that its continuation may put the fetus at risk for hypothyroidism. TRAb measurement also can be used during the third trimester to assess the risk of delayed neonatal hyperthyroidism when the mother continues to need MMI to control hyperthyroidism up to term. After delivery, MMI delivered to the fetus via placental passage is rapidly metabolized by the neonate, whereas the maternal TRAb disappears more slowly, with a half-life of around 3 weeks. Thus, a high level of TRAb in the mother in late pregnancy is an indicator that the neonate may need to be monitored for the onset of neonatal hyperthyroidism starting a few days after birth.

Technical remarks: A sensitive TBII assay or TSI assay should be used to detect TRAb during pregnancy.

A summary of TRAb measurement and management of hyperthyroidism caused by GD during pregnancy is presented in Table 9.

[S4] Postpartum thyroiditis

■ **RECOMMENDATION 78**

In women with thyrotoxicosis after delivery, selective diagnostic studies should be performed to distinguish postpartum thyroiditis from postpartum GD. **1/+00**

Postpartum thyroid dysfunction occurs in up to 10% of pregnancies in the United States. Postpartum thyroiditis is an autoimmune disorder unmasked in predisposed women as immune surveillance rebounds after pregnancy. The classic triphasic pattern is thyrotoxicosis at 1–6 months postpartum, followed by hypothyroidism and return to euthyroidism at 9–12 months postpartum (304,305). However, this sequence is not observed in every patient. Among 371 cases in 13 studies, 25% of patients were found to have a triphasic pattern, 43% had hypothyroidism without preceding thyrotoxicosis, and 32% had thyrotoxicosis without subsequent hypothyroidism (305). In a prospective study of pregnant women, those with positive thyroperoxidase (TPO) antibodies in the first trimester were 27 times more likely to develop postpartum thyroiditis than were those with negative serology (306). In this study, tobacco smoking and bottle feeding (maybe because of higher exposure of the maternal thyroid to iodine, which is not excreted into breast milk) also increased the risk of developing thyroiditis.

Postpartum thyroiditis must be distinguished from GD to recommend proper therapy. Goiter is generally more pronounced in GD, and thyroid bruit or GO strongly suggest GD as well. TRAb may be measurable in patients with postpartum thyroiditis, but higher titers are suggestive of GD. When *in vivo* testing is required to make this distinction, ^{123}I or technetium should be used rather than ^{131}I in women who are nursing, since the shorter half-life of these agents will allow breast milk to be pumped and discarded

Table 9. Summary of Recommendations Concerning Management of Graves' Disease in Pregnancy

Timing of diagnosis	*Specific circumstances*	*Recommendations*
GD diagnosed during pregnancy	Diagnosed during first trimester	Begin propylthiouracil[a] Measure TRAb at diagnosis and, if elevated, repeat at 22–26 weeks of gestation[b] If thyroidectomy is required, it is optimally performed during the second trimester
	Diagnosed after first trimester	Begin methimazole[c] Measure TRAb at diagnosis and, if elevated, repeat at 22–26 weeks of gestation[b] If thyroidectomy is required, it is optimally performed during the second trimester
GD diagnosed and treated prior to pregnancy	Currently taking methimazole	Switch to propylthiouracil as soon as pregnancy is confirmed with early testing[a] Measure TRAb either initially at 22–26 weeks of gestation, or initially during the first trimester and, if elevated, again at 22–26 weeks of gestation[b]
	In remission after stopping antithyroid medication Previous treatment with radioiodine or surgery	TRAb measurement not necessary Measure TRAb either initially at 22–26 weeks of gestation, or initially during the first trimester and, if elevated, again at 22–26 weeks of gestation[b]

[a]See remarks under Recommendation 71 for discussion regarding switching from one antithyroid drug to the other during pregnancy.
[b]If a TRAb-positive woman becomes TRAb-negative during pregnancy, this may indicate a need to reduce or stop antithyroid drug therapy to avoid fetal hypothyroidism. If the antithyroid drug treated mother has high TRAb values in late pregnancy this indicates a risk of delayed neonatal hyperthyroidism (see remarks to Recommendation 77). If the mother has undergone some type of thyroid ablation (radioactive iodine or surgery) for GD and TRAb is high, evaluate fetus carefully for hyperthyroidism in second half of pregnancy and adjust or begin antithyroid drug therapy accordingly.
[c]Avoid fetal hypothyroidism, especially in second half of pregnancy (see recommendation 75 for details).

for several days and nursing resumed, whereas breast-feeding should not be resumed if ^{131}I is given as treatment for GD (307). Total T_3 to T_4 ratios (ng/dL:mcg/dL) tend to be higher (>20) in patients with GD than in those with postpartum thyroiditis.

■ **RECOMMENDATION 79**
In women with symptomatic postpartum thyrotoxicosis, the judicious use of beta-adrenergic blocking agents is recommended. **1/+00**

Treatment for postpartum thyroiditis is generally supportive in nature, with the use of beta-adrenergic blockers such as propranolol (lowest level in breast milk) (308) or metroprolol to control pulse rate and hyperadrenergic symptoms during the thyrotoxic stage. Levothyroxine therapy may be beneficial, at least transiently, for women with symptomatic hypothyroidism or having TSH levels > 10 mU/L (305).

Technical remarks: Because beta blockers are secreted into breast milk in very low levels, no special monitoring is needed for breastfed infants of mothers on these medications (308).

[T] How should hyperthyroidism be managed in patients with Graves' ophthalmopathy?

GO is an inflammatory eye disease that develops in the orbit in association with autoimmune thyroid disorders (309). In the majority of cases, it occurs in patients with current or past GD. Thyroid-associated orbitopathy, thyroid eye disease, and Graves' orbitopathy are other names used for GO. Approximately half of patients with Graves' hyperthyroidism have signs and/or symptoms of GO, and 5% suffer from severe disease.

[T1] Assessment of disease activity and severity

The natural history of the disease is one of rapid deterioration followed by gradual improvement toward the baseline. This active phase is best described by the Clinical Activity Score (CAS) (310,311). The CAS is generated by the addition of one point for each of the following features if present: pain in primary gaze, pain with eye movement, chemosis, eyelid swelling, eyelid erythema, conjunctival redness, caruncula swelling, and, over the prior 3 months, decreased visual acuity, increased diplopia, and proptosis (Table 10). The score ranges from 0 to 10 and predicts response to anti-inflammatory therapies (310,311). A 7-point scale, lacking the last three elements, is used when no previous assessment is available. GO is considered active in patients with a CAS ≥ 3. Therefore, hyperthyroid patients having only lid retraction alone, or in conjunction with mild conjunctival erythema and eyelid swelling, are not considered to have active GO.

The severity of the disease is best assessed using objective, quantifiable parameters and is a useful tool for directing therapy. The main gradations of disease severity are mild, moderate to severe, and sight threatening (312). Table 11 lists the elements as agreed upon in a consensus statement by the European Group on Graves' Orbitopathy (EUGOGO) (312). Both activity and severity of the disease must be considered in therapeutic decisions regarding treatment of the eye disease itself, as well as treatment of hyperthyroidism. The overall evaluation and management of GO is best done in a multidisciplinary clinic combining endocrinologists and ophthalmologists with expertise

Table 10. Assessment of Graves' Ophthalmopathy: Clinical Activity Score Elements

Elements[a]	*Each visit*	*Comparison with previous visit*	*Score*
Painful feeling behind the globe over last 4 weeks	X		1
Pain with eye movement during last 4 weeks	X		1
Redness of the eyelids	X		1
Redness of the conjunctiva	X		1
Swelling of the eyelids	X		1
Chemosis (edema of the conjunctiva)	X		1
Swollen caruncle (fleshy body at medial angle of eye)	X		1
Increase in proptosis ≥2 mm		X	1
Decreased eye movements ≥5° any direction		X	1
Decreased visual acuity ≥1 line on Snellen chart		X	1

Adapted from Mourits et al., 1989 (310); and Mourits et al., 1997 (311).
[a]A 7-point scale (excluding the last three elements) is used when no previous assessment is available. GO is considered active in patients with a CAS ≥3.

Table 11. Graves' Ophthalmopathy Severity Assessment

Grade[a]	*Lid retraction*	*Soft tissues*	*Proptosis*[b]	*Diplopia*	*Corneal exposure*	*Optic nerve status*
Mild	<2 mm	Mild involvement	<3 mm	Transient or absent	Absent	Normal
Moderate	≥2 mm	Moderate involvement	≥3 mm	Inconstant	Mild	Normal
Severe	≥2 mm	Severe involvement	≥3 mm	Constant	Mild	Normal
Sight threatening	—	—	—	—	Severe	Compression
Upper limits of normal						
African American		F/M = 23/24 mm				
White		F/M = 19/21 mm				
Asian		F/M = 16/17 mm (Thai) or 18.6 mm (Chinese)				

Adapted from de Juan et al., 1980 (313); Sarinnapakorn et al., 2007 (314); Tsai et al., 2006 (315); and Bartalena et al., 2008 (312).
[a]**Mild GO**: patients whose features of GO have only a minor impact on daily life, generally insufficient to justify immunosuppressive or surgical treatment. **Moderate-to-severe GO**: patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). **Sight-threatening GO**: patients with dysthyroid optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.
[b]Proptosis refers to the variation compared to the upper limit of normal for each race/sex or the patient's baseline, if available.

in the condition and other specialties in consultation (e.g., ENT, radiation therapy, plastic surgery, and endocrine surgery).

QoL is clearly impaired by the disease, but only a limited number of articles have been published in this area. The U.S. Food and Drug Administration has endorsed QoL information as a component of any therapeutic application. The QoL correlation with disease severity has been fair to excellent for the one instrument published to date in a North American population (316), though it lacks prospective data. Two new validated instruments assessing QoL in the U.S. population are soon to be published and will be useful, as the instrument commonly used in Europe (317) has not been tested in the North American population.

In the remainder of section T, we discuss the prevention of GO and the management of hyperthyroidism in patients having established GO. In particular, we focus on recommendations regarding the concurrent use of corticosteroids in patients choosing radioactive iodine as treatment for hyperthyroidism (Table 12).

[T2] Prevention of GO

Current therapeutic approaches to GO, including local measures, corticosteroids, orbital radiation, and surgery (312), often fail to significantly improve the QoL of patients with this debilitating condition. Therefore, efforts should be made to prevent the development or progression of GO in patients with Graves' hyperthyroidism. Identified risk factors for GO include radioiodine therapy for hyperthyroidism (318,319), smoking, high pretreatment T_3 values (≥325 ng/dL or ≥5 nmol/L) (319), high serum pretreatment TRAb levels (>50% TBII inhibition or TSI > 8.8 IU/Liter) (320), and hypothyroidism following radioiodine treatment (321).

■ **RECOMMENDATION 80**

Euthyroidism should be expeditiously achieved and maintained in hyperthyroid patients with GO or risk factors for the development of ophthalmopathy. **1/++0**

A number of studies have suggested that development of persistent, untreated hypothyroidism after therapy for hyperthyroidism plays a detrimental role in the progression of GO. An early study noted that patients who were either hypo- or hyperthyroid had more severe GO than euthyroid patients (322). Subsequently, two cohort studies in which patients received levothyroxine therapy early after radioactive iodine with the specific intent of preventing hypothyroidism noted that deterioration of GO rarely occurred (0%-2%) (321,323). A randomized study of newly diagnosed GD found that radioactive iodine did not increase the risk of worsening GO compared to therapy with MMI (RR of 0.95) in the setting where hypothyroidism was actively prevented by administration of thyroid hormone at 2 weeks after radioactive iodine administration (49).

■ **RECOMMENDATION 81**

In nonsmoking patients with Graves' hyperthyroidism who have no clinically apparent ophthalmopathy, ^{131}I therapy without concurrent steroids, methimazole, or thyroidectomy should be considered equally acceptable therapeutic options. **1/++0**

Several retrospective cohort studies and randomized trials have identified the risk of GO development or progression after therapy for hyperthyroidism to be between 15% and 33%. Two randomized controlled trials found that risk to be 23/150 (15%) for radioactive iodine, compared with 4/148 (3%) for ATDs (318) in one study, and 13/39 (33%) for radioactive iodine compared with 4/38 (10%)

Table 12. Use of Oral Glucocorticoids for Prevention of Graves' Ophthalmopathy Development or Progression When Radioactive Iodine Is Used to Treat Graves' Hyperthyroidism[a]

	RAI without glucocorticoids	*RAI with oral glucocorticoids*
No GO (nonsmoker)	Recommend	Recommend against
No GO (smoker)	Insufficient data to recommend for or against	
GO present-active and mild (nonsmoker)	Acceptable[b]	Acceptable[b]
GO present-active and mild (smoker)	Recommend Against	Recommend
GO present-active and moderate-to-severe or sight-threatening (smoker or nonsmoker)	Recommend Against	Insufficient data to recommend for or against
GO present-inactive (smoker or nonsmoker)	Recommend	Recommend against

[a]Methimazole or thyroidectomy are also recommended treatment options in each of these scenarios, and they are the preferred choice of therapy in patients with active and moderate-to-severe or sight-threatening GO.
[b]The decision regarding use of concurrent glucocorticoids should be made in light of the risk-benefit ratio relative to the patient's overall health. Risk factors for GO deterioration (high T_3 level, high TRAb level, smoking) increase the benefit of glucocorticoids in preventing GO deterioration. Poorly controlled diabetes, osteoporosis, psychiatric illness, high risk for infections increase the likelihood of complications from glucocorticoids.

for ATDs and 6/37 (16%) for surgery (319) in the other study. In contrast, one prospective but nonrandomized cohort study identified no difference among ATD, surgery, and radioactive iodine treatment, with an overall 4.9%–7.1% frequency of GO development (324). The higher risk of GO worsening after radioactive iodine therapy in the majority of studies may be related to the unique increase in TRAb levels observed following this therapy (222). Experimental evidence suggests that these antibodies may be directly involved in GO pathogenesis (309).

There is evidence that corticosteroids given concurrently with radioiodine therapy may prevent worsening of GO in patients with mild active eye disease (318). However, there is insufficient evidence to recommend prophylactic treatment with corticosteroids in nonsmoking patients who do not have clinically apparent GO. The relatively low absolute risk of nonsmokers developing new-onset severe GO suggests that GO prevention should not be a factor in the selection of therapy for hyperthyroidism in this group of patients (318).

There is insufficient evidence to recommend for or against the use of prophylactic corticosteroids in smokers who have no evidence of GO. However, in two different studies, active smokers who received radioactive iodine represented the group with the highest incidence (23%–40%) of new GO or deterioration of pre-existing GO during 1 year of follow-up (49,318).

■ **RECOMMENDATION 82**
Clinicians should advise patients with GD to stop smoking and refer them to a structured smoking cessation program. Patients exposed to secondhand smoke should be identified and advised of its negative impact. **1/++0**

Smoking is the most important known risk factor for the development or worsening of GO, unrelated to type of therapy for GO (322), and consistent data from several studies show a detrimental effect of smoking on GO in patients treated with radioactive iodine (49,318). The risk is proportional to the number of cigarettes smoked per day and former smokers have significantly lower risk than current smokers, even after adjusting for lifetime cigarette consumption (325).

Technical remarks: Clinicians should consult guidelines on effective and evidence-based approaches to aid in smoking cessation and avoidance of secondhand smoke (326,327).

[T3] Treatment of hyperthyroidism in patients with active GO of mild severity (see Tables 10 and 11 for definitions of disease activity and severity)

■ **RECOMMENDATION 83**
In patients with Graves' hyperthyroidism who have mild active ophthalmopathy and no risk factors for deterioration of their eye disease, ^{131}I therapy, methimazole, and thyroidectomy should be considered equally acceptable therapeutic options. **1/++0**

■ **RECOMMENDATION 84**
Patients with Graves' hyperthyroidism and mild active ophthalmopathy who have no other risk factors for

deterioration of their eye disease and choose radioactive iodine therapy should be considered for concurrent treatment with corticosteroids. **2/++0**

Technical remarks: The decision whether or not to administer concurrent glucocorticoids in a particular patient choosing ^{131}I therapy should be made in light of the risk–benefit ratio (i.e., their personal risk of worsening GO, balanced against their risk of developing glucocorticoid side effects). Risk factors for side effects of oral corticosteroids include poorly controlled diabetes, hypertension, osteoporosis, psychiatric disease, and predisposition to infections. Smokers in whom the risk–benefit ratio for the concurrent use of corticosteroids is high may be better treated with methimazole or surgery. Besides smoking, risk factors for deterioration of GO following radioiodine therapy include high pretreatment T_3 values (≥325 ng/dL or ≥5 nmol/L) (319), active and progressive GO over the preceding 3 months, high serum pretreatment thyrotropin antibody levels (>50% TBII inhibition or TSI >8.8 IU/L), and development of hypothyroidism following the treatment (321).

The recommended corticosteroid dose for GO prophylaxis is the equivalent of prednisone 0.4–0.5 mg/kg/day, started 1–3 days after radioactive iodine treatment, continued for 1 month, and then tapered over 2 months (312). However, a recent retrospective cohort study suggested that lower doses and shorter duration of oral prednisone (about 0.2 mg/kg/day for 6 weeks) may be equally effective for prevention of GO exacerbation in patients with initially mild or absent eye disease, if supported by future randomized clinical trials (328).

■ **RECOMMENDATION 85**

Patients with Graves' hyperthyroidism and mild active ophthalmopathy who are smokers or have other risk factors for GO and choose radioactive iodine therapy should receive concurrent corticosteroids. **1/++0**

A randomized study of patients having pre-existing GO of mild severity found the relative risk for deterioration of eye disease to be 2.2 for surgery and 1.9 for radioactive iodine compared with ATDs, though the patients were not randomized with respect to their baseline GO status (319). An earlier prospective cohort (also not randomized as to baseline GO or smoking status and in which post-treatment hypothyroidism was not actively prevented) identified no difference in deterioration of pre-existing GO between the three modes of therapy (324). Neither surgery nor radioactive iodine therapy was associated with deterioration in pre-existing GO in 48 patients in another early study (329). One large randomized controlled trial studying mainly patients with previously treated GD showed radioactive iodine therapy to be associated with an increased risk of GO progression (RR of 5.8 in comparison with ATDs) and found that risk to be eliminated with concurrent corticosteroid administration (318).

[T4] Treatment of hyperthyroidism in patients with active and moderate-to-severe or sight-threatening GO (see Tables 10 and 11 for definitions of disease activity and severity)

■ **RECOMMENDATION 86**

Patients with Graves' hyperthyroidism and active moderate-to-severe or sight-threatening ophthalmopathy should be treated with either methimazole or surgery. **1/+00**

We are aware of no trials in patients with moderate-to-severe and active eye disease that compare hyperthyroidism therapies for impact on GO. However, a comparison of two different surgical approaches (total thyroidectomy vs. subtotal thyroidectomy) for patients with moderate-to-severe GO showed that the eye disease improved over 3 years of follow-up in all patients (330). In another series of 42 patients with progressive GO treated with total thyroidectomy, exophthalmos was stable in 60% of cases and improved in the remainder (331), suggesting that surgery is not detrimental to GO and may be associated with improvement in some patients. Other studies suggest that ATDs may not adversely impact mild active GO, but do not address severe GO (318).

Technical remarks: Radioactive iodine therapy is a less desirable option in these patients and, if used, concurrent steroids should be administered.

[T5] Treatment of GD in patients with inactive GO (see Table 10 for definition of disease inactivity)

■ **RECOMMENDATION 87**

In patients with Graves' hyperthyroidism and inactive ophthalmopathy, we suggest that ^{131}I therapy without concurrent corticosteroids, methimazole, and thyroidectomy are equally acceptable therapeutic options. **2/++0**

A series of 72 patients with inactive GO according to the CAS were treated with radioactive iodine without concurrent glucocorticoid administration (323). In those whom hypothyroidism was prevented by early thyroxine therapy, no deterioration in eye disease was reported (323). Smoking history did not impact GO outcome in this cohort. A recent retrospective study examined the impact of concurrent oral or intravenous glucocorticoid therapy on the prevalence of reactivation of GO after radioiodine therapy in patients having inactive GO (332). They identified GO activation in approximately 7% of patients considered at low risk who were given no steroid prophylaxis. Despite

prophylaxis, 33% of patients considered at high risk who were treated with oral glucocorticoids had worsening of GO. Only intravenous glucocorticoids were effective in preventing GO reactivation. However, because of the retrospective nature of this study and the lack of prespecified criteria for dose and route of steroid use in those considered at risk, we did not include these data in our deliberations regarding the above recommendation.

[U] How should overt drug-induced thyrotoxicosis be managed?

Although numerous medications may affect thyroid function or cause abnormal thyroid testing results (333), relatively few of these actually cause thyrotoxicosis. For those that do, three mechanisms are involved: (i) iodine-induced thyrotoxicosis; (ii) destructive thyroiditis; and (iii) induction of thyroid autoimmunity (GD or painless thyroiditis). More than one pathway has been identified for several medications. A summary of drugs causing thyrotoxicosis, the proposed mechanism(s), approximate timing of onset, duration, and therapeutic options is provided in Table 13.

[U1] Iodine-induced hyperthyroidism

Iodine-induced hyperthyroidism is believed to occur in patients with underlying thyroid autonomy, especially those living in areas with mild-to-moderate iodine deficiency. In one study of 788 patients undergoing cardiac angiography, none of the 27 with a suppressed TSH at baseline developed overt hyperthyroidism, and only 2 patients with no apparent risk factors became hyperthyroid (334). A retrospective study found that 7 of 28 elderly patients with hyperthyroidism had a history of recent iodine exposure (335), and a prospective study found that 2 of 73 patients developed hyperthyroidism after radiographic contrast (336). High iodine intake may also be followed by relapse of hyperthyroidism in patients with previous GD who are in remission after ATD therapy. In a small study of 10 patients, 2 had relapse of overt hyperthyroidism, and 2 developed SH after stopping high iodine intake (337).

■ **RECOMMENDATION 88**
Beta-adrenergic blocking agents alone or in combination with methimazole should be used to treat overt iodine-induced hyperthyroidism. **1/+00**

Table 13. Causes of Drug-Associated Thyrotoxicosis

Drug	*Mechanism(s)*	*Timing of onset following initiation of the drug*	*Therapy*
Amiodarone	Iodine induced (type 1)	Months to Years	Supportive care[a] Antithyroid drugs; perchlorate[b] Surgery
	Thyroiditis (type 2)	Often >1 year	Supportive care[a] Corticosteroids Surgery
Lithium	Painless thyroiditis	Often >1 year	Supportive care[a] Antithyroid drugs
Interferon α	Painless thyroiditis; GD	Months	Supportive care[a] Antithyroid drugs and/or radioactive iodine (GD only)
Interleukin-2	Painless thyroiditis; GD	Months	Supportive care[a] Antithyroid drugs and/or radioactive iodine (GD only)
Iodinated contrast	Underlying thyroid autonomy	Weeks to months	Antithyroid drugs
Radioactive iodine, early	Destruction	1–4 weeks	Observation; if severe, administer corticosteroids
Radioactive iodine for TMNG, late	GD	3–6 months	Antithyroid drugs Repeat radioactive iodine Surgery

[a]Supportive care may include beta-adrenergic blockers during the thyrotoxic stage and levothyroxine if hypothyroidism develops.
[b]Not available in the United States.

Iodine-induced hyperthyroidism (the Jod-Basedow phenomenon) is usually self-limited, lasting 1–18 months (335,338). Treatment includes avoidance of additional iodine and administration of beta-blockers alone or with ATDs, depending on the severity of hyperthyroidism. Radioactive iodine is not an option until the iodine load has been cleared, which may take several months depending on the length of exposure to iodine. Surgery may be used in patients allergic or resistant to antithyroid drugs.

Technical remarks: Dosing of MMI for iodine-induced thyrotoxicosis is 20–40 mg daily, given either as a daily or twice-daily dosing. There may be relative resistance to antithyroid drugs in patients with iodine-induced hyperthyroidism. Urinary iodine may be monitored to assess the rate of clearance of the iodine load.

[U2] Cytokine-induced thyrotoxicosis

■ **RECOMMENDATION 89**
Patients who develop thyrotoxicosis during therapy with interferon-α or interleukin-2 should be evaluated to determine etiology (thyroiditis vs. GD) and treated accordingly. **1/+00**

Interferon-α (IFN-α)- and interleukin-2-treated patients are at increased risk for developing thyrotoxicosis, especially those with pre-existing thyroid autoimmunity. Thyrotoxicosis in this setting can be due to either painless thyroiditis or GD (339). In a literature review, 69% of patients with IFN-α-associated thyrotoxicosis were deemed to have GD as the etiology (340).

A meta-analysis found that 46% of patients with positive pretreatment thyroid peroxidase antibodies (TPO Ab) developed thyroid dysfunction after IFN-α therapy for hepatitis C infection, compared to only 5% of those with negative antibodies (341).

[U3] Amiodarone-induced thyrotoxicosis

■ **RECOMMENDATION 90**
We suggest monitoring thyroid function tests before and at 1 and 3 months following the initiation of amiodarone therapy, and at 3–6 month intervals thereafter. **2/+00**

Amiodarone is a drug frequently used in the treatment of refractory atrial or ventricular tachyarrhymias. Amiodarone-induced thyrotoxicosis (AIT) occurs in up to 6% of patients taking this medication in iodine-sufficient areas of the world (18,342,343) and in up to 10% in iodine-deficient areas, such as parts of Europe (344).

■ **RECOMMENDATION 91**
We suggest testing to distinguish type 1 (iodine-induced) from type 2 (thyroiditis) varieties of amiodarone-induced thyrotoxicosis. **1/+00**

Two basic mechanisms have been identified in the development of AIT, including an iodine-induced form of hyperthyroidism (type 1 AIT, or goitrous AIT) due to the high iodine content of amiodarone (37% by molecular weight), and type 2 AIT, which is a destructive thyroiditis. Type 1 AIT tends to occur in patients with underlying thyroid autonomy in a nodular goiter, but the term is also used when amiodarone use is associated with GD, whereas type 2 AIT is due to a direct destructive effect of amiodarone on thyrocytes. RAIU is occasionally measurable in type 1 AIT (particularly in regions of iodine deficiency), but not in type 2 AIT. Increased vascular flow on color-flow Doppler ultrasound study may be seen in patients with type 1 AIT, but not type 2 AIT. Measurement of serum interleukin-6 levels does not reliably distinguish between the two types of AIT (345). The distinction between type 1 AIT and type 2 AIT is not always clear, and some patients have elements of both types (18).

■ **RECOMMENDATION 92**
The decision to stop amiodarone in the setting of thyrotoxicosis should be determined on an individual basis in consultation with a cardiologist, based on the presence or absence of effective alternative antiarrhythmic therapy. **1/+00**

The need for amiodarone discontinuation is controversial because (i) this drug is frequently the only medication able to control cardiac arrhythmia, (ii) the effects of this fat soluble drug may persist for many months, and (iii) amiodarone may have T_3-antagonistic properties at the cardiac level and inhibit T_4 to T_3 conversion, such that withdrawal may actually aggravate cardiac manifestations of thyrotoxicosis (18,342). In addition, type 2 AIT typically resolves even if amiodarone therapy is continued.

■ **RECOMMENDATION 93**
Methimazole should be used to treat type 1 amiodarone-induced thyrotoxicosis and corticosteroids should be used to treat type 2 amiodarone-induced thyrotoxicosis. **1/+00**

■ **RECOMMENDATION 94**
Combined antithyroid drug and anti-inflammatory therapy should be used to treat patients with overt amiodarone-induced thyrotoxicosis who fail to respond to single modality therapy, and patients in whom the type of disease cannot be unequivocally determined. **1/+00**

Type 1 AIT is best treated with MMI (40 mg daily) to prevent new hormone synthesis and, rarely, with added potassium perchlorate (250 mg four times daily; not available in the United States) (346). Type 2 AIT is better treated with anti-inflammatory therapy such as prednisone (40 mg daily) with improvement occasionally seen as early as 1 week, and usually within a few weeks (346).

In one study, 20 patients with AIT, including both type 1 and type 2 subtypes, were treated with perchlorate for 1 month to inhibit thyroid iodide transport, resulting in euthyroidism in 12 patients (7 with type 1 AIT and 5 with type 2 AIT). Corticosteroids were then given to the eight nonresponders, and euthyroidism was achieved in all after an average of approximately 6 weeks (347). When a clear distinction between type 1 AIT and type 2 AIT is not possible, a combination of prednisone and methimazole should be used until the patient has stabilized, at which time the drugs may be individually tapered. Thyroidectomy may be required in patients who prove refractory to medical therapy (348).

Technical remarks: The suggested starting dose of MMI in this setting is 40 mg once daily until the patient is euthyroid (generally 3–6 months). If high doses of MMI continue to be required, splitting the dose may be more effective. The suggested dose of corticosteroids in this setting is equivalent to 40 mg prednisone given once daily for 2–4 weeks, followed by a gradual taper over 2–3 months, based on the patient's clinical response.

■ **RECOMMENDATION 95**

Patients with amiodarone-induced thyrotoxicosis who are unresponsive to aggressive medical therapy with methimazole and corticosteroids should undergo thyroidectomy. **1/+00**

Technical remarks: Patients with AIT who fail to respond to medical therapy should be offered thyroidectomy before they become excessively debilitated from inadequately controlled thyrotoxicosis. The patient should be counseled that while thyroidectomy in this setting carries with it significant morbidity and a high mortality rate (9%), delay or deferral of surgery imparts an even higher risk of death (348). Thyroidectomy done under regional anesthesia when available may be preferred (18,349).

[V] How should thyrotoxicosis due to destructive thyroiditis be managed?

Several varieties of thyroiditis can present with thyrotoxicosis, including postpartum thyroiditis, painless thyroiditis, drug-induced thyroiditis, subacute thyroiditis, traumatic thyroiditis, and acute thyroiditis. In general, thyroid dysfunction caused by thyroiditis is less severe than that seen with other forms of endogenous thyrotoxicosis; RAIU is universally low during the thyrotoxic stage, owing to leaking of thyroid hormone with suppression of serum TSH concentrations.

[V1] Subacute thyroiditis

The diagnosis of subacute thyroiditis in a thyrotoxic patient should be made based on clinical history, physical examination, and RAIU. Subacute thyroiditis presents with moderate-to-severe pain in the thyroid, often radiating to the ears, jaw, or throat. The pain may begin focally and spread throughout the gland over several weeks. Patients may have malaise, low-grade fever, and fatigue in addition to the symptoms of thyrotoxicosis. The thyroid is firm and painful to palpation. In addition to laboratory evidence of thyrotoxicosis, the erythrocyte sedimentation rate or C-reactive protein is elevated, and mild anemia is common. RAIU is low, and thyroid ultrasonography shows diffuse heterogeneity and decreased or normal color-flow Doppler, rather than the enhanced flow characteristic of GD.

■ **RECOMMENDATION 96**

Patients with mild symptomatic subacute thyroiditis should be treated initially with beta-adrenergic-blocking drugs and nonsteroidal anti-inflammatory agents. Those failing to respond or those with moderate-to-severe symptoms should be treated with corticosteroids. **1/+00**

Subacute thyroiditis is treated with beta-blockers and anti-inflammatory therapy. Nonsteroidal anti-inflammatory agents (NSAIDs) provide pain relief in patients with mild symptoms due to subacute thyroiditis, and should be considered first-line therapy in such patients. Patients who fail to respond to full doses of NSAIDs over several days should be treated instead with corticosteroid therapy, such as prednisone 40 mg daily for 1–2 weeks followed by a gradual taper over 2–4 weeks or longer, depending upon clinical response. A retrospective review of patients receiving care for subacute thyroiditis found that patients treated with corticosteroids had more rapid resolution of pain (mean duration, 8 days) compared with those treated with NSAIDs (mean duration, 35 days). However, symptoms can recur as the dose of corticosteroid is reduced (19). As with painless and postpartum thyroiditis, levothyroxine may be employed during the hypothyroid stage, but should be withdrawn after 3–6 months with recovery of normal function verified by thyroid function testing.

[V2] Painless thyroiditis

Painless or silent thyroiditis is an autoimmune disease manifested by positive anti-TPO antibodies in the majority of patients, and a triphasic pattern in some cases. The

postpartum period is the most common time when painless thyroiditis is seen, but painless thyroiditis can also occur in nonpregnant patients and men. Painless thyroiditis has been described in some types of drug-induced thyroid dysfunction, including that associated with lithium or cytokine therapy. The latter includes IFN-α or interleukin-2 (discussed elsewhere), but not IFN-β therapy. Beta-adrenergic blockers can be used to treat thyrotoxic symptoms in patients with painless thyroiditis, but antithyroid drugs have no utility, since new hormone synthesis is already low in these patients. Rarely, corticosteroids have been used to ameliorate the severity and the time course of thyrotoxicosis due to painless thyroiditis (350), but they should be reserved only for more severe cases. Some patients may have recurrent episodes of painless thyroiditis, separated by years.

[V3] Acute thyroiditis

Patients with acute thyroiditis (also referred to as suppurative thyroiditis or thyroid abscess) are generally euthyroid. However, on occasion, the condition presents as destructive thyrotoxicosis (351). The etiology of acute thyroiditis is most frequently a bacterial infection affecting the thyroid, either through hematogenous spread or direct extension through a fistula from an infected pyriform sinus. Therapy involves systemic antibiotics as well as abscess drainage or removal, and excision or occlusion of the offending pyriform sinus. Thyrotoxicosis should be treated symptomatically with beta-blocking agents. As in other forms of destructive thyroiditis, there is no role for antithyroid drugs.

[W] How should thyrotoxicosis due to unusual causes be managed?

These are several unusual causes of thyrotoxicosis that should be considered in the differential diagnosis (Table 14). Since effective treatment depends on accurate diagnosis, it is important to clearly identify the etiology in every patient presenting with thyrotoxicosis.

[W1] TSH-secreting pituitary tumors

Functional pituitary tumors secreting TSH are rare. In a multicenter review of 4400 pituitary tumors seen over a 25-year period, 43 (1%) were TSH-secreting adenomas (33). The majority of patients present with diffuse goiter and clinical signs of thyrotoxicosis. In addition, serum TSH levels may be elevated or, especially in patients who have not had thyroid ablation, they may be inappropriately normal. Cosecretion of either prolactin or growth hormone occurs in up to 25% of cases; 1%–2% secrete both growth hormone and prolactin, and a similar percentage cosecrete gonadotropins. Most TSH-producing adenomas are larger than 1 cm, and approximately 40% of patients have associated visual field deficits (352).

■ **RECOMMENDATION 97**

The diagnosis of TSH-secreting pituitary tumor should be based on an inappropriately normal or elevated serum TSH level associated with elevated free T_4 estimates and T_3 concentrations, usually associated with the presence of a pituitary tumor on MRI and the absence of a family history or genetic testing consistent with thyroid hormone resistance in a thyrotoxic patient. **1/+00**

Distinction between a TSH-secreting adenoma and thyroid hormone resistance is important, since thyroid function test results are similar, yet management is quite different for these two disorders. TSH-secreting adenomas are more likely to have concurrent alpha-subunit elevation (not useful in postmenopausal women due to concurrent gonadotropin elevation), a blunted TSH response to thyrotropin-releasing hormone (TRH) (when available), elevated sex-hormone-binding globulin and resting energy expenditure, and clinical evidence of thyrotoxicosis, as well as an anatomic abnormality on MRI of the pituitary.

Technical remarks: Genetic testing for thyroid hormone resistance is commercially available and may be

Table 14. Unusual Causes of Thyrotoxicosis

Disorder	*Diagnosis*	*Primary management*
TSH-producing adenoma	Pituitary MRI, alpha-subunit to TSH ratio	Surgical removal
Struma ovarii	Radioiodine uptake over pelvis	Surgical removal
Choriocarcinoma	Elevation in the absence of pregnancy	Surgical removal
Thyrotoxicosis factitia (surreptious LT_4 or LT_3)	Absence of goiter; suppressed thyroglobulin	Psychosocial evaluation
Functional thyroid cancer metastases	Whole-body radioiodine scanning	Radioiodine ablation, embolization and/or surgical removal

useful in equivocal cases, especially in those patients without family members available for thyroid function testing.

Surgery is generally the mainstay of therapy for TSH-producing pituitary tumors. The patient should be made euthyroid preoperatively. Long-term ATD therapy should be avoided. Preoperative adjunctive therapy with octreotide and dopamine agonist therapy has been examined. Treatment with octreotide results in a >50% reduction in serum TSH values in the majority of patients treated, and a concurrent return to euthyroidism in most (33). A reduction in tumor size has been observed in 20%–50% of patients treated with octreotide (33,352), but less impressive results have been obtained with bromocriptine therapy (352). Sterotactic or conventional radiotherapy has also been used in cases that prove refractory to medical therapy. For patients with TSH-producing adenomas who are considered poor surgical candidates, primary medical therapy with octreotide can be considered.

■ **RECOMMENDATION 98**
Patients with TSH-secreting pituitary adenomas should undergo surgery performed by an experienced pituitary surgeon. **1/+00**

Technical remarks: Postoperative adjunctive therapy with octreotide and/or external beam radiation therapy may be useful in managing patients with persistent central hyperthyroidism after a debulking procedure for nonresectable TSH-secreting adenomas (33).

[W2] Struma ovarii

■ **RECOMMENDATION 99**
Patients with struma ovarii should be treated initially with surgical resection. **1/+00**

Struma ovarii, defined as ectopic thyroid tissue existing as a substantial component of an ovarian tumor, is quite rare, representing <1% of all ovarian tumors. Approximately 5%–10% of patients with struma ovarii present with thyrotoxicosis (353) due to either autonomous ectopic thyroid function or the coexistence of GD, and up to 25% of struma ovarii tumors contain elements of papillary thyroid cancer. Patients previously treated for GD may have persistent or recurrent hyperthyroidism due to the action of TRAb on the ectopic thyroid tissue (354). Treatment of struma ovarii generally involves surgical removal, performed largely due to the risk of malignancy within the struma tissue and of curing the hyperthyroidism. Preoperative treatment with beta-adrenergic-blocking agents and antithyroid drugs is warranted to restore euthyroidism before surgery.

Technical remarks: In cases of suspected metastatic malignant struma ovarii, radioactive iodine is generally given following surgical removal of both the ovarian tumor and the patient's thyroid to facilitate delivery of isotope to any potential residual malignant cells.

[W3] Choriocarcinoma

■ **RECOMMENDATION 100**
Treatment of hyperthyroidism due to choriocarcinoma should include both methimazole and treatment directed against the primary tumor. **1/+00**

Patients with choriocarcinoma, including molar pregnancy and testicular cancer, may present with thyrotoxicosis due to the effect of tumor-derived hCG upon the TSH receptor (355,356). This cross-stimulation only occurs at very high levels of hCG, since hCG is only a weak agonist for the TSH receptor. Treatment of hyperthyroidism due to choriocarcinoma involves both treatment directed against the primary tumor and treatment designed to prevent the thyroid from responding to hCG stimulation, such as with antithyroid drugs.

[W4] Thyrotoxicosis factitia

Thyrotoxicosis factitia includes all causes of thyrotoxicosis due to the ingestion of thyroid hormone. This may include intentional ingestion of thyroid hormone either surreptitiously or iatrogenically, as well as unintentional ingestion either accidentally, such as in pediatric poisoning or pharmacy error, or through ingestion of supplements that contain thyroid extracts. Historically, accidental thyroid hormone ingestion has occurred as a result of eating meat contaminated with animal thyroid tissue ("hamburger thyrotoxicosis") (357). Whereas iatrogenic causes of thyrotoxicosis factitia are easily identified, surreptitious use of thyroid hormone may present a diagnostic quandary. Clues to this diagnosis are an absence of goiter, a suppressed serum thyroglobulin level, and a decreased uptake of radioactive iodine. A disportionately elevated T_3 level suggests that the patient may be ingesting liothyronine or a combination T_4/T_3 preparation.

[W5] Functional thyroid cancer metastases

Thyrotoxicosis due to functional metastases in patients with thyroid cancer has been described in a handful of cases. Typically, patients have either a very large primary follicular cancer or widely metastatic follicular thyroid cancer, and may have coexisting TRAb as the proximate cause of the thyrotoxicosis (358). More recently, thyrotoxicosis has been reported following multiple injections of recombinant human TSH in patients with metastatic thyroid cancer in preparation for imaging. In general, functioning metastasis are treated with radioactive iodine with the addition of ATDs as needed for persistent hyperthyroidism.

Recombinant human TSH should be avoided in these patients.

ACKNOWLEDGMENTS

The task force wishes to thank Ms. Bobbi Smith, Executive Director, ATA, and Ms. Sheri Slaughter, Assistant to the task force, for their expert help and support.

DISCLOSURE

Disclosure Information for 2 years before May 2010 and the known future as of May 2010. D.R. is a consultant for Abbott Laboratories and has received research grant support from Genzyme. For all other authors, no competing financial interests exist.

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Appendix A. Hyperthyroidism Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists: Summary of Recommendations

[A] **Background**

[B] **How should clinically or incidentally discovered thyrotoxicosis be evaluated and initially managed?**

Recommendation 1	A radioactive iodine uptake should be performed when the clinical presentation of thyrotoxicosis is not diagnostic of GD; a thyroid scan should be added in the presence of thyroid nodularity. 1/+00
Recommendation 2	Beta-adrenergic blockade should be given to elderly patients with symptomatic thyrotoxicosis and to other thyrotoxic patients with resting heart rates in excess of 90 bpm or coexistent cardiovascular disease. 1/++0
Recommendation 3	Beta-adrenergic blockade should be considered in all patients with symptomatic thyrotoxicosis. 1/+00

[C] **How should overt hyperthyroidism due to GD be managed?**

Recommendation 4	Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: ^{131}I therapy, antithyroid medication, or thyroidectomy. 1/++0

[D] **If ^{131}I therapy is chosen as treatment for GD, how should it be accomplished?**

Recommendation 5	Patients with GD who are at increased risk for complications due to worsening of hyperthyroidism (i.e., those who are extremely symptomatic or have free T_4 estimates 2–3 times the upper limit of normal) should be treated with beta-adrenergic blockade prior to radioactive iodine therapy. 1/+00
Recommendation 6[a]	Pretreatment with methimazole prior to radioactive iodine therapy for GD should be considered in patients who are at increased risk for complications due to worsening of hyperthyroidism (i.e., those who are extremely symptomatic or have free T_4 estimate 2–3 times the upper limit of normal). 2/+00
Recommendation 7	Medical therapy of any comorbid conditions should be optimized prior to administering radioactive iodine. 1/+00
Recommendation 8	Sufficient radiation should be administered in a single dose (typically 10–15 mCi) to render the patient with GD hypothyroid. 1/++0
Recommendation 9	A pregnancy test should be obtained within 48 hours prior to treatment in any female with childbearing potential who is to be treated with radioactive iodine. The treating physician should obtain this test and verify a negative result prior to administering radioactive iodine. 1/+00
Recommendation 10	The physician administering the radioactive iodine should provide written advice concerning radiation safety precautions following treatment. If the precautions cannot be followed, alternative therapy should be selected. 1/+00
Recommendation 11	Follow-up within the first 1–2 months after radioactive iodine therapy for GD should include an assessment of free T_4 and total T_3. If the patient remains thyrotoxic, biochemical monitoring should be continued at 4–6 week intervals. 1/+00

Recommendation 12 When hyperthyroidism due to GD persists after 6 months following ^{131}I therapy, or if there is minimal response 3 months after therapy, retreatment with ^{131}I is suggested. 2/+00

[E] **If antithyroid drugs are chosen as initial management of GD, how should the therapy be managed?**

Recommendation 13 Methimazole should be used in virtually every patient who chooses antithyroid drug therapy for GD, except during the first trimester of pregnancy when propylthiouracil is preferred, in the treatment of thyroid storm, and in patients with minor reactions to methimazole who refuse radioactive iodine therapy or surgery. 1/++0

Recommendation 14 Patients should be informed of side effects of antithyroid drugs and the necessity of informing the physician promptly if they should develop pruritic rash, jaundice, acolic stools or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, or pharyngitis. Before starting antithyroid drugs and at each subsequent visit, the patient should be alerted to stop the medication immediately and call their physician when there are symptoms suggestive of agranulocytosis or hepatic injury. 1/+00

Recommendation 15 Prior to initiating antithyroid drug therapy for GD, we suggest that patients have a baseline complete blood count, including white count with differential, and a liver profile including bilirubin and transaminases. 2/+00

Recommendation 16 A differential white blood cell count should be obtained during febrile illness and at the onset of pharyngitis in all patients taking antithyroid medication. Routine monitoring of white blood counts is not recommended. 1/+00

Recommendation 17 Liver function and hepatocellular integrity should be assessed in patients taking propylthiouracil who experience pruritic rash, jaundice, light colored stool or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea, or fatigue. 1/+00

Recommendation 18 Minor cutaneous reactions may be managed with concurrent antihistamine therapy without stopping the antithyroid drug. Persistent minor side effects of antithyroid medication should be managed by cessation of the medication and changing to radioactive iodine or surgery, or switching to the other antithyroid drug when radioactive iodine or surgery are not options. In the case of a serious allergic reaction, prescribing the alternative drug is not recommended. 1/+00

Recommendation 19 If methimazole is chosen as the primary therapy for GD, the medication should be continued for approximately 12–18 months, then tapered or discontinued if the TSH is normal at that time. 1/+++

Recommendation 20 Measurement of TRAb levels prior to stopping antithyroid drug therapy is suggested, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating greater chance for remission. 2/+00

Recommendation 21 If a patient with GD becomes hyperthyroid after completing a course of methimazole, consideration should be given to treatment with radioactive iodine or thyroidectomy. Low-dose methimazole treatment for longer than 12–18 months may be considered in patients not in remission who prefer this approach. 2/+00

[F] **If thyroidectomy is chosen for treatment of GD, how should it be accomplished?**

Recommendation 22 Whenever possible, patients with GD undergoing thyroidectomy should be rendered euthyroid with methimazole. Potassium iodide should be given in the immediate preoperative period. 1/+00

Recommendation 23 In exceptional circumstances, when it is not possible to render a patient with GD euthyroid prior to thyroidectomy, the need for thyroidectomy is urgent, or when the patient is allergic to antithyroid medication, the patient should be adequately treated with beta-blockade and potassium iodide in the immediate preoperative period. The surgeon and anesthesiologist should have experience in this situation. 1/+00

Recommendation 24 If surgery is chosen as the primary therapy for GD, near-total or total thyroidectomy is the procedure of choice. 1/++0

Recommendation 25 If surgery is chosen as the primary therapy for GD, the patient should be referred to a high-volume thyroid surgeon. 1/++0

Recommendation 26 Following thyroidectomy for GD, we suggest that serum calcium or intact parathyroid hormone levels be measured, and that oral calcium and calcitriol supplementation be administered based on these results. 2/+00

Recommendation 27 Antithyroid drugs should be stopped at the time of thyroidectomy for GD, and beta-adrenergic blockers should be weaned following surgery. 1/+00

Recommendation 28 Following thyroidectomy for GD, L-thyroxine should be started at a daily dose appropriate for the patient's weight (0.8 μg/lb or 1.7 μg/kg), and serum TSH measured 6–8 weeks postoperatively. 1/+00

[G] **How should thyroid nodules be managed in patients with GD?**

Recommendation 29 If a thyroid nodule is discovered in a patient with GD, the nodule should be evaluated and managed according to recently published guidelines regarding thyroid nodules in euthyroid individuals. 1/++0

[H] **How should thyroid storm be managed?**

Recommendation 30 A multimodality treatment approach to patients with thyroid storm should be used, including beta-adrenergic blockade, antithyroid drug therapy, inorganic iodide, corticosteroid therapy, aggressive cooling with acetaminophen and cooling blankets, volume resuscitation, respiratory support and monitoring in an intensive care unit. 1/+00

[I] **How should overt hyperthyroidism due to TMNG or TA be treated?**

Recommendation 31 We suggest that patients with overtly TMNG or TA be treated with either ^{131}I therapy or thyroidectomy. On occasion, long term, low-dose treatment with methimazole may be appropriate. 2/++0

[J] **If ^{131}I therapy is chosen as treatment for TMNG or TA, how should it be accomplished?**

Recommendation 32 Patients with TMNG or TA who are at increased risk for complications due to worsening of hyperthyroidism, including the elderly and those with cardiovascular disease or severe hyperthyroidism, should be treated with beta-blockade prior to radioactive iodine therapy and until euthyroidism has been achieved. 1/+00

Recommendation 33[b] Pretreatment with methimazole prior to radioactive iodine therapy for TMNG or TA should be considered in patients who are at increased risk for complications due to worsening of hyperthyroidism, including the elderly and those with cardiovascular disease or severe hyperthyroidism. 2/+00

Recommendation 34 Nonfunctioning nodules on radionuclide scintigraphy or nodules with suspicious ultrasound characteristics should be managed according to recently published guidelines regarding thyroid nodules in euthyroid individuals. 1/++0

Recommendation 35 For radioactive iodine treatment of TMNG, sufficient radiation should be administered in a single dose to alleviate hyperthyroidism. 1/++0

Recommendation 36 For radioactive iodine treatment of TA, sufficient radiation to alleviate hyperthyroidism should be administered in a single dose. 1/++0

Recommendation 37 Follow-up within the first 1–2 months after radioactive iodine therapy for TMNG or TA should include an assessment of free T_4, total T3 and TSH. This should be repeated at 1–2 month intervals until stable results are obtained, then at least annually thereafter according to clinical indication. 1/+00

Recommendation 38 If hyperthyroidism persists beyond 6 months following ^{131}I therapy for TMNG or TA, retreatment with radioactive iodine is suggested. 2/+00

[K] **If surgery is chosen for treatment of TMNG or TA, how should it be accomplished?**

Recommendation 39 If surgery is chosen as treatment for TMNG or TA, patients with overt hyperthyroidism should be rendered euthyroid prior to the procedure with methimazole pretreatment (in the absence of allergy to the medication), with or without beta-adrenergic blockade. Preoperative iodine should not be used in this setting. 1/+00

Recommendation 40 If surgery is chosen as treatment for TMNG, near- total or total thyroidectomy should be performed. 1/++0

Recommendation 41 Surgery for TMNG should be performed by a high-volume thyroid surgeon. 1/++0

Recommendation 42 If surgery is chosen as the treatment for TA, an ipsilateral thyroid lobectomy, or isthmusectomy if the adenoma is in the thyroid isthmus, should be performed. 1/++0

Recommendation 43 We suggest that surgery for TA be performed by a high-volume surgeon. 2/++0

Recommendation 44 Following thyroidectomy for TMNG, we suggest that serum calcium or intact parathyroid hormone levels be measured, and that oral calcium and calcitriol supplementation be administered based on these results. 2/+00

Recommendation 45 Methimazole should be stopped at the time of surgery for TMNG or TA. Beta-adrenergic blockade should be slowly discontinued following surgery. 1/+00

Recommendation 46 Following surgery for TMNG, thyroid hormone replacement should be started at a dose appropriate for the patient's weight (0.8 mcg/lb or 1.7 mcg/kg) and age, with elderly patients needing somewhat less. TSH should be measured every 1–2 months until stable, and then annually. 1/+00

Recommendation 47 Following surgery for TA, TSH and estimated free T_4 levels should be obtained 4–6 weeks after surgery, and thyroid hormone supplementation started if there is a persistent rise in TSH above the normal range. 1/+00

Recommendation 48 Radioactive iodine therapy should be used for retreatment of persistent or recurrent hyperthyroidism following inadequate surgery for TMNG or TA. 1/+00

[L] **Is there a role for antithyroid drug therapy in patients with TMNG or TA?**

Recommendation 49 We suggest that long-term methimazole treatment of TMNG or TA be avoided, except in some elderly or otherwise ill patients with limited longevity who are able to be monitored regularly, and in patients who prefer this option. 2/+00

[M] **Is there a role for radiofrequency, thermal or alcohol ablation in the management of TA or TMNG?**

[N] **How should GD be managed in children and adolescents?**

Recommendation 50 Children with GD should be treated with methimazole, ^{131}I therapy, or thyroidectomy. ^{131}I therapy should be avoided in very young children (<5 years). ^{131}I therapy in patients between 5 and 10 years of age is acceptable if the calculated ^{131}I administered activity is <10 mCi. ^{131}I therapy in patients older than 10 years of age is acceptable if the activity is >150 uCi/g of thyroid tissue. Thyroidectomy should be chosen when definitive therapy is required, the child is too young for ^{131}I, and surgery can be performed by a high-volume thyroid surgeon. 1/++0

[O] **If antithyroid drugs are chosen as initial management of GD in children, how should the therapy be managed?**

Recommendation 51 Methimazole should be used in virtually every child who is treated with antithyroid drug therapy. 1/++0

Recommendation 52 Pediatric patients and their caretakers should be informed of side effects of antithyroid drugs and the necessity of stopping the medication immediately and informing their physician if they develop pruritic rash, jaundice, acolic stools or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, or pharyngitis. 1/+00

Recommendation 53 Prior to initiating antithyroid drug therapy, we suggest that pediatric patients have, as a baseline, complete blood cell count, including white blood cell count with differential, and a liver profile including bilirubin, transaminases, and alkaline phosphatase. 2/+00

Recommendation 54 Beta adrenergic blockade is recommended for children experiencing symptoms of hyperthyroidism, especially those with heart rates in excess of 100 beats per minute. 1/+00

Recommendation 55 Antithyroid medication should be stopped immediately, and white blood counts measured in children who develop fever, arthralgias, mouth sores, pharyngitis, or malaise. 1/+00

Recommendation 56 When propylthiouracil is used in children, the medication should be stopped immediately and liver function and hepatocellular integrity assessed in children who experience anorexia, pruritis, rash, jaundice, light-colored stool or dark urine, joint pain, right upper quadrant pain or abdominal bloating, nausea or malaise. 1/+00

Recommendation 57 Persistent minor cutaneous reactions to methimazole therapy in children should be managed by concurrent antihistamine treatment or cessation of the medication and changing to therapy with radioactive iodine or surgery. In the case of a serious allergic reaction to an antithyroid medication, prescribing the other antithyroid drug is not recommended. 1/+00

Recommendation 58 If methimazole is chosen as the first-line treatment for GD in children, it should be administered for 1–2 years and then discontinued, or the dose reduced, to assess whether the patient is in remission. 1/++0

Recommendation 59 Pediatric patients with GD who are not in remission following 1–2 years of methimazole therapy should be considered for treatment with radioactive iodine or thyroidectomy. 1/+00

[P] **If radioactive iodine is chosen as treatment for GD in children, how should it be accomplished?**

Recommendation 60 We suggest that children with GD having total T_4 levels of >20 ug/dL (200 nmol/L) or free T_4 estimates >5 ng/dL (60 pmol/L) who are to receive radioactive iodine therapy be pretreated with methimazole and beta-adrenergic blockade until total T_4 and/or free T_4 estimates normalize before proceeding with radioactive iodine. 2/+00

Recommendation 61 If ^{131}I therapy is chosen as treatment for GD in children, sufficient ^{131}I should be administered in a single dose to render the patient hypothyroid. 1/++0

[Q] **If thyroidectomy is chosen as treatment for GD in children, how should it be accomplished?**

Recommendation 62 Children with GD undergoing thyroidectomy should be rendered euthyroid with the use of methimazole. Potassium iodide should be given in the immediate preoperative period. 1/+00

Recommendation 63 If surgery is chosen as therapy for GD in children, total or near-total thyroidectomy should be performed. 1/++0

Recommendation 64 Thyroidectomy in children should be performed by high-volume thyroid surgeons. 1/++0

[R] **How should SH be managed?**

Recommendation 65 When TSH is persistently <0.1 mU/L, treatment of SH should be strongly considered in all individuals ≥65 years of age, and in postmenopausal women who are not on estrogens or bisphosphonates; patients with cardiac risk factors, heart disease or osteoporosis; and individuals with hyperthyroid symptoms. 2/++0

Recommendation 66 When TSH is persistently below the lower limit of normal but >0.1 mU/L, treatment of SH should be considered in individuals ≥65 years of age and in patients with cardiac disease or symptoms of hyperthyroidism. 2/+00

Recommendation 67 If SH is to be treated, the treatment should be based on the etiology of the thyroid dysfunction and follow the same principles as outlined for the treatment of overt hyperthyroidism. 1/+00

[S] **How should hyperthyroidism in pregnancy be managed?**

Recommendation 68 The diagnosis of hyperthyroidism in pregnancy should be made using serum TSH values, and either total T_4 and T_3 with total T_4 and T_3 reference range adjusted at 1.5 times the nonpregnant range or free T_4 and free T_3 estimations with trimester-specific normal reference ranges. 1/+00

Recommendation 69 Transient hCG-mediated thyrotropin suppression in early pregnancy should not be treated with antithyroid drug therapy. 1/+00

Recommendation 70 Antithyroid drug therapy should be used for hyperthyroidism due to GD that requires treatment during pregnancy. Propylthiouracil should be used when antithyroid drug therapy is started during the first trimester. Methimazole should be used when antithyroid drug therapy is started after the first trimester. 1/+00

Recommendation 71 We suggest that patients taking methimazole who decide to become pregnant obtain pregnancy testing at the earliest suggestion of pregnancy and be switched to propylthiouracil as soon as possible in the first trimester and changed back to methimazole at the beginning of the second trimester. Similarly, we suggest that patients started on propylthiouracil during the first trimester be switched to methimazole at the beginning of the second trimester. 2/+00

Recommendation 72 GD during pregnancy should be treated with the lowest possible dose of antithyroid drugs needed to keep the mother's thyroid hormone levels slightly above the normal range for total T_4 and T_3 values in pregnancy and the TSH suppressed. Free T_4 estimates should be kept at or slightly above the upper limit of the nonpregnant reference range. Thyroid function should be assessed monthly, and the antithyroid drug dose adjusted as required. 1/+00

Recommendation 73 When thyroidectomy is necessary for the treatment of hyperthyroidism during pregnancy, the surgery should be performed if possible during the second trimester. 1/+00

Recommendation 74 TRAb levels should be measured when the etiology of hyperthyroidism in pregnancy is uncertain. 1/+00

Recommendation 75 Patients who were treated with radioactive iodine or thyroidectomy for GD prior to pregnancy should have TRAb levels measured using a sensitive assay either initially at 22–26 weeks of gestation,or initially during the first trimester and, if elevated, again at 22–26 weeks of gestation. 1/+00

Recommendation 76 Patients found to have GD during pregnancy should have TRAb levels measured at diagnosis using a sensitive assay and, if elevated, again at 22–26 weeks of gestation. 1/+00

Recommendation 77 TRAb levels measured at 22–26 weeks of gestation should be used to guide decisions regarding neonatal monitoring. 1/+00

Recommendation 78 In women with thyrotoxicosis after delivery, selective diagnostic studies should be performed to distinguish postpartum thyroiditis from postpartum GD. 1/+00

Recommendation 79 In women with symptomatic postpartum thyrotoxicosis, the judicious use of beta-adrenergic blocking agents is recommended. 1/+00

[T] **How should hyperthyroidism be managed in patients with Graves' ophthalmopathy?**

Recommendation 80 Euthyroidism should be expeditiously achieved and maintained in hyperthyroid patients with Graves' ophthalmopathy or risk factors for the development of ophthalmopathy. 1/++0

Recommendation 81 In nonsmoking patients with Graves' hyperthyroidism who have no clinically apparent ophthalmopathy, ^{131}I therapy without concurrent steroids, methimazole or thyroidectomy should be considered equally acceptable therapeutic options. 1/++0

Recommendation 82 Clinicians should advise patients with GD to stop smoking and refer them to a structured smoking cessation program. Patients exposed to secondhand smoke should be identified and advised of its negative impact. 1/++0

Recommendation 83 In patients with Graves' hyperthyroidism who have mild active ophthalmopathy and no risk factors for deterioration of their eye disease, ^{131}I therapy, methimazole, and thyroidectomy should be considered equally acceptable therapeutic options. 1/++0

Recommendation 84 Patients with Graves' hyperthyroidism and mild active ophthalmopathy who have no other risk factors for deterioration of their eye disease and choose radioactive iodine therapy should be considered for concurrent treatment with corticosteroids. 2/++0

Recommendation 85 Patients with Graves' hyperthyroidism and mild active ophthalmopathy who are smokers or have other risk factors for Graves' ophthalmopathy and choose radioactive iodine therapy should receive concurrent corticosteroids. 1/++0

Recommendation 86 Patients with Graves' hyperthyroidism and active moderate-to-severe or sight-threatening ophthalmopathy should be treated with either methimazole or surgery. 1/+00

Recommendation 87 In patients with Graves' hyperthyroidism and inactive ophthalmopathy, we suggest that ^{131}I therapy without concurrent corticosteroids, methimazole, and thyroidectomy are equally acceptable therapeutic options. 2/++0

[U] **How should overt drug-induced thyrotoxicosis be managed?**

Recommendation 88 Beta-adrenergic blocking agents alone or in combination with methimazole should be used to treat overt iodine-induced hyperthyroidism. 1/+00

Recommendation 89 Patients who develop thyrotoxicosis during therapy with interferon-α or interleukin-2 should be evaluated to determine etiology (thyroiditis vs. GD) and treated accordingly. 1/+00

Recommendation 90 We suggest monitoring thyroid function tests before and at 1 and 3 months following the initiation of amiodarone therapy, and at 3–6-month intervals thereafter. 2/+00

Recommendation 91 We suggest testing to distinguish type 1 (iodine-induced) from type 2 (thyroiditis) varieties of amiodarone-induced thyrotoxicosis. 1/+00

Recommendation 92 The decision to stop amiodarone in the setting of thyrotoxicosis should be determined on an individual basis in consultation with a cardiologist, based on the presence or absence of effective alternative antiarrhythmic therapy. 1/+00

Recommendation 93 Methimazole should be used to treat type 1 amiodarone-induced thyrotoxicosis and corticosteroids should be used to treat type 2 amiodarone-induced thyrotoxicosis. 1/+00

Recommendation 94 Combined antithyroid drug and anti-inflammatory therapy should be used to treat patients with overt amiodarone-induced thyrotoxicosis who fail to respond to single modality therapy, and patients in whom the type of disease cannot be unequivocally determined. 1/+00

	Recommendation 95	Patients with amiodarone-induced thyrotoxicosis who are unresponsive to aggressive medical therapy with methimazole and corticosteroids should undergo thyroidectomy. 1/+00
[V]	**How should thyrotoxicosis due to destructive thyroiditis be managed?**	
	Recommendation 96	Patients with mild symptomatic subacute thyroiditis should be treated initially with beta-adrenergic-blocking drugs and nonsteroidal anti-inflammatory agents. Those failing to respond or those with moderate-to-severe symptoms should be treated with corticosteroids. 1/+00
[W]	**How should thyrotoxicosis due to unusual causes be managed?**	
	Recommendation 97	The diagnosis of TSH-secreting pituitary tumor should be based on an inappropriately normal or elevated serum TSH level associated with elevated free T_4 estimates and T_3 concentrations, usually associated with the presence of a pituitary tumor on MRI and the absence of a family history or genetic testing consistent with thyroid hormone resistance in a thyrotoxic patient. 1/+00
	Recommendation 98	Patients with TSH-secreting pituitary adenomas should undergo surgery performed by an experienced pituitary surgeon. 1/+00
	Recommendation 99	Patients with struma ovarii should be treated initially with surgical resection. 1/+00
	Recommendation 100	Treatment of hyperthyroidism due to choriocarcinoma should include both methimazole and treatment directed against the primary tumor. 1/+00

[a]Task force opinion was not unanimous; one person held the opinion that pretreatment with methimazole is not necessary in this setting.

[b]Task force opinion was not unanimous; one member held the opinion that pretreatment with methimazole in patients already treated with beta adrenergic blockade is not indicated in this setting.

GD, Graves' disease; SH, subclinical hyperthyroidism; T_3, triiodothyronine; T_4, thyroxine; TA, toxic adenoma; TMNG, toxic multinodular goiter; TRAb, thyrotropin receptor antibody; TSH, thyroid-stimulating hormone.