2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis

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Background: 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 subspecialty physicians and others providing care for patients with this condition.

Methods: The American Thyroid Association (ATA) previously co-sponsored guidelines for the management of thyrotoxicosis that were published in 2011. Considerable new literature has been published since 2011, the ATA felt updated evidence-based guidelines were needed, and 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 update the 2011 text and 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' orbitopathy; and management of other miscellaneous causes of thyrotoxicosis. New

paradigms since publication of the 2011 guidelines are presented for the evaluation of the etiology of thyrotoxicosis, the management of Graves' hyperthyroidism with antithyroid drugs, the management of pregnant hyperthyroid patients, and the preparation of patients for thyroid surgery. The sections on less common causes of thyrotoxicosis have been expanded.

Conclusions: One hundred twenty-four 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.

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 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 (ATDs) 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 subspecialty 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 thyrotoxicosis were published previously by the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) in 2011 , the ATA determined that thyrotoxicosis represents a priority area in need of updated evidence-based practice guidelines.

The target audience for these guidelines includes general and subspecialty 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 selected a chairperson to lead the task force and this individual (D.S.R.) identified the other 10 members of the panel in consultation with the

ATA board 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 North America, South America, and Europe. 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.

The task force reviewed the 2011 guidelines and published editorials regarding those guidelines, and developed a revised 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. One task force member was assigned as the primary writer for each topic. One or more task force members were assigned as secondary writers for each topic, providing their specific expertise and critical review for the primary writer. The relevant literature was reviewed using a systematic PubMed search for primary references and reviews published after the submission of the 2011 guidelines, supplemented with additional published materials found on focused PubMed searches. Recommendations were 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 primary writer 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. Task force deliberations took place **between**

2014 and 2016 during several lengthy committee meetings, 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 (3-6). 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 (7). 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 as 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), or a weak recommendation or a suggestion that may not be appropriate for every patient, depending on context, patient values, and preferences. The quality of the evidence is indicated as low-quality evidence, moderate-quality evidence, or high-quality evidence, based on consistency of results between studies and study design, limitations, and the directness of the evidence. In several instances, the evidence was insufficient to recommend for or against a test or a treatment, and the task force made a statement labeled “no recommendation.” 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 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.

Results

[A] Background

[A1] Causes of thyrotoxicosis

In general, thyrotoxicosis can occur if (i) the thyroid is excessively stimulated by trophic factors; (ii) there is constitutive 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).

Hyperthyroidism is generally considered overt or subclinical, depending on the **biochemical** severity of the hyperthyroidism, although in reality the disease represents a continuum of overactive thyroid function. Overt hyperthyroidism is defined as a **subnormal (usually undetectable)** serum thyroid-stimulating hormone (TSH) with elevated serum levels of triiodothyronine (T_3) and/or free thyroxine estimates (free T_4). Subclinical hyperthyroidism is defined as a low or undetectable serum TSH with values within the normal reference range for both T_3 and free T_4. Both overt and subclinical disease may lead to characteristic signs and symptoms, although subclinical hyperthyroidism is usually considered more mild. Overzealous or suppressive thyroid hormone administration may cause either type of thyrotoxicosis, particularly subclinical thyrotoxicosis. Endogenous overt or subclinical thyrotoxicosis is caused by excess thyroid hormone production and release or by inflammation and release of hormone by the gland.

Endogenous hyperthyroidism is most commonly due to Graves' Disease (GD) or nodular thyroid disease. GD is an autoimmune disorder in which thyrotropin receptor antibodies (TRAb) stimulate the TSH receptor, increasing thyroid hormone production and release. The development of nodular thyroid disease includes growth of established nodules, new nodule formation, and development of autonomy over time (8). In toxic adenomas (TA), autonomous hormone production can be caused by somatic activating mutations of genes regulating thyroid growth and hormone synthesis. Germline mutations in the gene encoding the TSH receptor can cause sporadic or familial nonautoimmune hyperthyroidism associated with a diffuse enlargement of the thyroid gland (9). Autonomous 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 (10). GD is the most common cause of hyperthyroidism in the United States (11,12). Although toxic nodular goiter is less common than GD, its prevalence increases with age and in the presence of dietary iodine deficiency. Therefore, toxic nodular goiter may actually be more common than GD in older patients, especially in regions of iodine deficiency (13,14). Unlike toxic nodular goiter, which is progressive (unless triggered by excessive iodine intake), remission of mild GD has been reported in up to 30% of patients without treatment (15).

Less common causes of thyrotoxicosis include the entities of painless and subacute thyroiditis, which occur due to inflammation of thyroid tissue with release of preformed hormone into the circulation. Painless thyroiditis caused by lymphocytic inflammation appears to occur with a different frequency depending on the population studied: in Denmark it accounted for only 0.5% of thyrotoxic patients, it was 6% of patients in Toronto and 22% of patients in Wisconsin (16-18).

Painless thyroiditis may occur during lithium (19), cytokine (e.g., interferon-alpha) (20), or tyrosine kinase inhibitor therapy (21), and in the postpartum period it is referred to as postpartum thyroiditis (22). A painless destructive thyroiditis (not usually lymphocytic) occurs in 5–10% of amiodarone-treated patients (23). Subacute thyroiditis is thought to be caused by viral infection and is characterized by fever and thyroid pain (24).

[A2] Clinical consequences of thyrotoxicosis

The cellular actions of thyroid hormone are mediated by T_3, the active form of thyroid hormone. T_3 binds to a specific nuclear receptor that regulates the expression of many genes. Non-genomic actions of thyroid hormone also regulate numerous important physiologic functions.

Thyroid hormone influences almost every tissue and organ system. 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 (25). Untreated **or partially treated** thyrotoxicosis is associated with loss of weight, osteoporosis, atrial fibrillation, embolic events, muscle weakness, tremor, neuropsychiatric symptoms and rarely cardiovascular collapse and death (26,27). There is only moderate correlation between **the degree of** thyroid hormone **elevation** and clinical signs and symptoms. Symptoms and signs that result from increased adrenergic stimulation include tachycardia and anxiety and may be more pronounced in younger patients and those with larger goiters (28). The signs and symptoms of mild, or subclinical, thyrotoxicosis are similar to those of overt thyrotoxicosis, but differ in magnitude. Measurable changes in basal metabolic rate, cardiovascular hemodynamics, and psychiatric and neuropsychological function can be present in mild thyrotoxicosis (29).

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

[B1] Assessment of disease severity

Assessment of thyrotoxic manifestations, and especially potential cardiovascular and neuromuscular complications, is essential in 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, in one small study of 25 patients with GD, the Hyperthyroid Symptom Scale did not strongly correlate with free T_4 or T_3 and was inversely correlated with age (28). The importance of age as a determinant of the prevalence and severity of hyperthyroid symptoms has been recently confirmed (30). Cardiac evaluation may be necessary, especially in the older patient, and may require an echocardiogram, electrocardiogram, Holter monitor, or myocardial perfusion studies (31). This should not postpone therapy of the thyrotoxicosis. In addition to the administration of beta-blockers (31), treatment may be needed for concomitant myocardial ischemia, congestive heart failure, or atrial arrhythmias (25). Anticoagulation may be necessary in patients in atrial fibrillation (32). Goiter size, obstructive symptoms, and the severity of Graves' orbitopathy (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, one should assess thyroid

size, tenderness, symmetry, and nodularity; pulmonary, cardiac, and neuromuscular function (29,31,33); and presence or absence of peripheral edema, eye signs, or pretibial myxedema.

[B2] Biochemical evaluation

Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected thyrotoxicosis and should be used as an initial screening test (34). However, when thyrotoxicosis is strongly suspected, diagnostic accuracy improves when a serum TSH, free T_4, and total T_3 are assessed at 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 (35).

In overt hyperthyroidism, serum free T_4 and/or T_3 are elevated, and serum TSH is **subnormal** (**usually** <0.01 mU/L in a third generation assay). In mild hyperthyroidism, serum T_4 and free T_4 can be normal, only serum T_3 may be elevated, and serum TSH will be low or undetectable. These laboratory findings have been called ‘‘T_3-toxicosis’’ and may represent the earliest stages of hyperthyroidism caused by Graves’ disease or an autonomously functioning thyroid nodule. As with T_4, total T_3 measurements are impacted by protein binding. Assays for estimating free T_3 are less widely validated and less robust than those for free T_4. Therefore, measurement of total T_3 is frequently preferred over free T_3 in clinical practice. Subclinical hyperthyroidism is defined as a

normal serum free T_4 and normal total T_3 or free T_3, with subnormal serum TSH concentration. Laboratory protocols that store sera and automatically retrieve the sample and add on free T_4 and total T_3 measurements when the initial 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, **or spurious assay results due to interfering antibodies,** a normal serum TSH level precludes the diagnosis of thyrotoxicosis. The term ‘‘euthyroid hyperthyroxinemia’’ has been used to describe a number of entities, primarily thyroid hormone-binding protein disorders, which cause elevated *total* serum T_4 concentrations (and frequently elevated total serum T_3 concentrations) in the absence of hyperthyroidism (36). These conditions include elevations in T_4 binding globulin (TBG) or transthyretin (TTR) (37); the presence of an abnormal albumin which binds T_4 with high capacity (familial dysalbuminemic hyperthyroxinemia); 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 (23) or high-dose propranolol (31), acute psychosis (38), extreme high altitude (39), and amphetamine abuse (40). Estimates of free thyroid hormone concentrations frequently also give erroneous results in these disorders. Spurious free T_4 elevations may occur from heterophilic antibodies or in the setting of heparin therapy, due to in vitro activation of lipoprotein lipase and release of free fatty acids that displace T_4 from its binding proteins.

Heterophilic antibodies can also cause spurious high TSH values, and this should be ruled out by repeating the TSH in another assay, measurement of TSH in serial dilution, or direct measurement of human anti-mouse antibodies (HAMA).

Ingestion of high doses of biotin may cause spurious results in assays that utilize a steptavidin-biotin separation technique (41,42). In immunometric assays, frequently used to measure TSH, excess biotin displaces biotinylated antibodies and causes spuriously low results, while in competitive binding assays, frequently used to measure free T_4, excess biotin competes with biotinylated analogue and results in falsely high results. Patients taking high doses of biotin or supplements containing biotin, who have elevated T_4 and suppressed TSH should stop taking biotin and have repeat measurements **at least** 2 days later.

After excluding euthyroid hyperthyroxinemia, TSH-mediated hyperthyroidism should be considered when thyroid hormone concentrations are elevated and TSH is normal or elevated. A pituitary lesion on MRI and a disproportionately high **ratio of the** serum level of the alpha-subunit of the pituitary glycoprotein hormones **to TSH** supports the diagnosis of a TSH-producing pituitary adenoma (43). A family history and genetic testing for mutations in the T_3-receptor supports the diagnosis of thyroid hormone resistance (44).

[B3] Determination of etiology

■ **RECOMMENDATION 1**

The etiology of thyrotoxicosis should be determined. If the diagnosis is not apparent based on the clinical presentation and initial biochemical evaluation, diagnostic testing is indicated and can include, depending on available expertise and resources, (1) measurement of TRAb, (2) determination of the radioactive iodine uptake (RAIU), or (3) measurement of thyroidal blood flow on ultrasonography. An iodine-123 or technetium-99m pertechnetate scan should be obtained when the clinical presentation suggests a toxic adenoma or toxic multinodular goiter. **Strong recommendation, moderate-quality evidence.**

In a patient with a symmetrically enlarged thyroid, recent onset of orbitopathy, and moderate to severe hyperthyroidism, the diagnosis of GD is likely and further evaluation of hyperthyroidism causation is unnecessary. In a thyrotoxic patient with a non-nodular thyroid and no definite orbitopathy, measurement of TRAb or a radioactive iodine uptake can be used to distinguish GD from other etiologies. In a study using a model of a theoretical population of 100,000 enrollees in a managed care organization in the United States, the use of TRAb measurements to diagnose GD **compared to RAIU measurements** reduced costs by 47% and resulted in a 46% quicker diagnosis (45).

A radioactive iodine uptake measures the percentage of administered radioiodine (RAI) that is concentrated into thyroid tissue after a fixed interval, usually 24 hours. Technetium uptake measurements utilize pertechnetate that is trapped by the thyroid, but not organified. A technetium (TcO_4) uptake measures the percentage of administered technetium that is trapped by the thyroid after a fixed interval, usually 20 minutes.

Uptake measurements are indicated when the diagnosis is in question (except during pregnancy and usually during lactation **(see section [T4])** and distinguishes causes of thyrotoxicosis having elevated or normal uptake over the thyroid gland from those with near-absent uptake (Table 3). Uptake 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 RAIU will be near zero in patients with painless, postpartum, or subacute thyroiditis, factitious ingestion of thyroid hormone or recent excess iodine intake. The RAIU may be low after exposure to iodinated contrast in the preceding 1–2 months or with ingestion of a diet unusually rich in iodine such as seaweed soup or kelp. However, RAIU is rarely **<1%** 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 from the clinical history), assessment of urinary iodine concentration **(spot urine iodine adjusted for urine creatinine concentration or a 24-hour urine iodine concentration)** may be helpful. The uptake over the neck will also be absent in a patient with struma ovarii, where the abnormal thyroid tissue is located in an ovarian teratoma.

Thyroid scans provide a planar image of the thyroid gland using a gamma camera, to assess potential variability in the concentration of the radioisotope within thyroid tissue. RAI scans may be obtained coincident with the RAIU and technetium scans may be obtained coincident with the technetium uptake. While technetium scans result in a low range of normal uptake and high background activity, total body radiation exposure is less than for ^{123}I scans; either type of scan can be useful in determining the etiology of hyperthyroidism in the presence of thyroid nodularity.

A thyroid scan should be obtained if the clinical presentation suggests a toxic adenoma or toxic multinodular goiter. 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. The image in TMNG demonstrates multiple areas of focal increased and suppressed uptake. If autonomy is extensive, the image may be difficult to distinguish from that of GD (46). Additionally, GD and non-toxic nodular goiter may coincide resulting in positive TRAb levels and a nodular ultrasound or heterogeneous uptake images (47).

Where expertise is available, ultrasonography with color Doppler flow can distinguish thyroid hyperactivity (increased flow) from destructive thyroiditis (48). Quantitative Doppler evaluation requires careful adjustments to prevent artifacts and measures the peak systolic velocity from intrathyroidal arteries or the inferior thyroidal artery (49). This test may be particularly useful when radioactive iodine is contraindicated, such as during pregnancy or breastfeeding. Doppler flow has also been used to distinguish between subtypes of amiodarone-induced thyrotoxicosis (see Section [V2]), and between GD and destructive thyroiditis (see Section [W2]).

The ratio of total T_3 to total T_4 can also be useful in assessing the etiology of thyrotoxicosis when scintigraphy is contraindicated. Because a hyperactive gland produces more T_3 than T_4, T_3 will be elevated above the upper limit of normal more than T_4 in thyrotoxicosis caused by hyperthyroidism, whereas T_4 is elevated more than T_3 in thyrotoxicosis caused by thyroiditis (50); in one study the ratio of total T_3/total T_4

(ng/mcg) was >20 in GD and toxic nodular goiter, and <20 in painless or postpartum thyroiditis (51). **A high T_4 to T_3 ratio may be seen in thyrotoxicosis factitia (from exogenous levothyroxine).**

The choice of initial diagnostic testing depends on cost, availability, and local expertise. TRAb is cost-effective because if it is positive it confirms the diagnosis of the most common cause of thyrotoxicosis, but if negative it does not distinguish among other etiologies, and it can be negative in very mild GD. If third generation TRAb assays are not readily available, RAIU is preferred for initial testing.

Diagnostic testing may be influenced by the choice of therapy (see Section [C]). For example, measuring TRAb in a patient with GD who plans on taking methimazole (MMI) with the hope of achieving a remission will provide a baseline measurement for disease activity. Obtaining a RAIU in a patient who prefers radioactive iodine treatment will provide both diagnostic information and facilitate the calculation of the radioactive iodine dose (see Section [D2]).

In most patients, 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 usually >50 and sometimes over 100 mm/h. Patients with painless thyroiditis **presenting within the first year after childbirth (postpartum thyroiditis)**, often have a personal or family history of autoimmune thyroid disease, and typically have measurable serum concentrations of antithyroid peroxidase antibodies (52).

Thyroglobulin is released along with thyroid hormone in subacute, painless, and palpation thyroiditis **(following manipulation of the thyroid gland during surgery),** whereas its release is suppressed in the setting of exogenous thyroid hormone administration. 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, a near-zero RAIU, **and a T_3 to T_4 ratio (ng/mcg) <20 if due to exogenous levothyroxine**. (53). In patients with antithyroglobulin antibodies, which interfere with thyroglobulin measurement, an alternative but not widely available approach is measurement of fecal T_4 **(54); mean values were 1.03 nmol/g in euthyroid patients, 1.93 nmol/g in Graves' hyperthyroidism, and 12-24 nmol/g in factitious throtoxicosis**.

Technical remarks: There are two methods for measuring TRAb (55). Third-generation TBI assays are competition-based assays which measure inhibition of binding of a labeled monoclonal anti-human TSHR antibody (or labeled TSH) to recombinant TSHR. Such assays detect blocking as well as neutral and stimulating immunoglobulins. The newer TSI assays detect increased cAMP production, e.g. from Chinese hamster ovary cells transfected with hTSHR, and are positive in 96% of patients with GD (56). Older TSI assays were more specific but less sensitive than TBI assays. In the setting of thyrotoxicosis, third generation TBI assays have a sensitivity of 97% and a specificity of 99% (57)

[B4] Symptomatic management

■ **RECOMMENDATION 2**

Beta-adrenergic blockade is recommended in all patients with symptomatic thyrotoxicosis, especially elderly patients and thyrotoxic patients with resting heart rates in excess of 90 bpm or coexistent cardiovascular disease. **Strong recommendation, moderate-quality evidence.**

In a randomized controlled trial of MMI alone versus MMI and a beta-adrenergic blocking agent, after 4 weeks, patients taking beta-adrenergic blockers had lower heart rates, less shortness of breath and fatigue and had improved "physical functioning" on the SF-36 health questionnaire (58).

Technical remarks: Since there is not sufficient β-1 selectivity of the available beta-blockers at the recommended doses, these drugs are generally contraindicated in patients with bronchospastic asthma. 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 relative β-1 selective agent can be used cautiously, with careful monitoring of pulmonary status (Table 4). 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 (31), but most often low to moderate doses (Table 4) give sufficient symptom relief. Oral administration of calcium channel blockers, both verapamil and diltiazem, have been shown to effect rate control in patients who do not tolerate or are not candidates for β-adrenergic blocking agents.

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

■ RECOMMENDATION 3

Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: Radioactive iodine therapy, antithyroid drugs, or thyroidectomy. **Strong recommendation, moderate-quality evidence.**

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: RAI therapy, ATDs, or thyroidectomy (59). In the United States, RAI has been the therapy most preferred by physicians but a trend has been present in recent years to increase use of ATDs **and reduce the use** of RAI. A 2011 survey of clinical endocrinologists showed that 59.7% of respondents from the United States selected RAI as primary therapy for an uncomplicated case of GD, compared to 69% in a similar survey performed 20 years earlier (60). In Europe, Latin America, and Japan, there has been a greater physician preference for ATDs (61). 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 (62). Currently, there is no scientific evidence to support the recommendation of alternative therapies for the treatment of hyperthyroidism (63).

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 costs (64). 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.

The treatment selection should also take into account the local availability and the associated costs. Whenever surgery is selected as treatment one should consider the use of expert high-volume thyroid surgeons with on average lower risk of complications; lack of that expertise should be considered against the known risk of alternative choices. Long term continuous treatment of hyperthyroidism with ATDs may be considered in selected cases (65,66).

Clinical situations that favor a particular modality as treatment for Graves' hyperthyroidism (Table 5):

a. RAI therapy: Women planning a pregnancy in the future (in more than 6 months following RAI administration, 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, **and patients with** contraindications to ATD use **or failure to achieve euthyroidism during treatment with ATDs**. Patients with periodic thyrotoxic hypokalemic paralysis, right heart failure pulmonary hypertension, or congestive heart failure should also be considered good candidates for RAI therapy.

b. ATDs: Patients with high likelihood of remission (patients, especially women, with mild disease, small goiters, and negative or low-titer TRAb); pregnancy; 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; patients with moderate to severe active GO; and patients who need more rapid biochemical disease control.

c. Surgery: Women planning a pregnancy in <6 months **provided thyroid hormone levels are normal** (i.e., possibly before thyroid hormone levels would be normal if RAI were chosen as therapy); 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 thyroid nodules especially **if greater than 4 cm or** if nonfunctioning, or hypofunctioning on iodine-123 or technetium-99m pertechnetate scanning; coexisting hyperparathyroidism requiring surgery; 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. RAI therapy: Definite contraindications include pregnancy, lactation, coexisting thyroid cancer, or suspicion of thyroid cancer, individuals unable to comply with radiation safety guidelines and used with **informed** caution in women planning a pregnancy within 4–6 months.

b. ATDs: Definite contraindications to 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, **or lack of access to a high volume thyroid surgeon.** Pregnancy is a relative contraindication and surgery should only be used in the 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 second trimester. Although it is the safest time, it is not without risk (4.5%–5.5% risk of preterm labor) (67,68). Thyroid surgery in pregnancy is also associated with a higher rate of complications, including hypoparathyroidism and recurrent laryngeal nerve injury (68).

Patient values that may impact choice of therapy:

a. RAI therapy: Patients choosing RAI 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 ATDs, 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 (69).

b. ATDs: Patients choosing ATD 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]), 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 RAI therapy is chosen, how should it be accomplished?

[D1] Preparation of patients with GD for RAI therapy

■ **RECOMMENDATION 4**

Because RAI treatment of GD can cause a transient exacerbation of hyperthyroidism, beta-adrenergic blockade should be considered even in asymptomatic patients who are at increased risk for complications due to worsening of hyperthyroidism, i.e., elderly patients and patients with co-morbidities. **Weak recommendation, low-quality evidence.**

■ **RECOMMENDATION 5**

In addition to beta-adrenergic blockade (see Recommendation 2 **and 4**), pretreatment with MMI prior to RAI therapy for GD should be considered in patients who are at increased risk for complications due to worsening of hyperthyroidism. MMI should be discontinued 2-3 days prior to RAI. **Weak recommendation, moderate-quality evidence.**

■ **RECOMMENDATION 6**

In patients who are at increased risk for complications due to worsening of hyperthyroidism, resuming MMI 3-7 days after RAI administration should be considered. **Weak recommendation, low-quality evidence.**

■ **RECOMMENDATION 7**

Medical therapy of any comorbid conditions should be optimized prior to RAI therapy. **Strong recommendation, low-quality evidence.**

RAI has been used to treat hyperthyroidism for more than seven decades. It is well tolerated and complications are rare, except for those related to orbitopathy (see section [U]). Thyroid storm occurs only rarely following the administration of RAI (70-72). In one study of patients with thyrotoxic cardiac disease treated with RAI as the sole modality, no clinical worsening in any of the cardinal symptoms of thyrotoxicosis was seen (73). However, RAI can induce a short-term increase of thyroid hormone levels (74,75). To prevent a clinical exacerbation of hyperthyroidism, the use of MMI or carbimazole, the latter of which is not marketed in the United States, before and after RAI treatment may be considered in patients with severe hyperthyroidism, the elderly,

and those with substantial comorbidity that puts them at greater risk for complications of worsening thyrotoxicosis (75,76). 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 (70). These comorbid conditions should be addressed with standard medical care and the patient rendered medically stable before the administration of RAI if possible. **If possible iodinated radiocontrast should be avoided.** In addition, beta-adrenergic blocking drugs should be used judiciously in these patients in preparation for RAI therapy (25,77). MMI (75) and carbimazole (78) have shown to reduce thyroid hormone levels after RAI treatment in randomized controlled trials. However, a recent meta-analysis of randomized controlled trials also found that MMI, carbimazole and propylthiouracil reduce the success rate if given in the week before or after RAI treatment (71). Use of higher activities of RAI may offset the reduced effectiveness of RAI therapy following antithyroid medication (75,76).

A special diet is not required before RAI therapy, but nutritional supplements that may contain excess iodine **and seaweeds** 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 RAI trapped.

Technical remarks: Patients that might benefit from adjunctive MMI or carbimazole may be those who are poorly tolerating hyperthyroid symptoms. Such patients frequently have free T_4 2–3 times the upper limit of normal. Young and middle aged, otherwise healthy patients who are clinically well-compensated despite significant

biochemical hyperthyroidism can generally receive RAI without pretreatment. If given as pretreatment, MMI and carbimazole should be discontinued before the administration of RAI. Discontinuation of **ATDs for** 2-3 days prevents a short-term increase of thyroid hormone levels (79), which is found after 6 days (75,76). In elderly patients or in those with underlying cardiovascular disease, resuming MMI or carbimazole 3-7 days after RAI administration should be considered, and generally tapered as thyroid function normalizes. In one study, if MMI was restarted 7 days after RAI, the free T_4 measured 3 weeks after RAI was 6% lower than the values at the time of RAI administration, and if MMI was not restarted after RAI, the free T_4 values were 36% higher than the values at the time of RAI administration (80). Over several decades, there have been reports that pretreatment with lithium reduces the activity of RAI necessary for cure of Graves' hyperthyroidism and may prevent the thyroid hormone increase seen upon ATD withdrawal (81-83). However, this is not used widely, and there is insufficient evidence to recommend the practice. In selected patients with Graves' hyperthyroidism who would have been candidates for pretreatment with ATDs due to comorbidities or excessive symptoms, but who are allergic to ATDs, the duration of hyperthyroidism may be shortened by administering iodine (e.g. SSKI) beginning one week after RAI administration (84).

[D2] Administration of RAI in the treatment of GD

■ **RECOMMENDATION 8**

Sufficient activity of RAI should be administered in a single application, typically **a mean dose of** 10–15 mCi (370-555 MBq), to render the patient with GD hypothyroid. **Strong recommendation, moderate-quality evidence.**

■ **RECOMMENDATION 9**

A pregnancy test should be obtained within 48 hours prior to treatment in any woman with childbearing potential who is to be treated with RAI. The treating physician should obtain this test and verify a negative result prior to administering RAI. **Strong recommendation, low-quality evidence**

The goal of RAI therapy in GD is to control hyperthyroidism by rendering the patient hypothyroid; this treatment is very effective, provided sufficient radiation dose 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 RAI (85).

The first method is simple, while the second method requires two unknowns to be determined: the uptake of RAI and the size of the thyroid. The therapeutic RAI activity can then be calculated using these two factors and the quantity of radiation (μCi or Bq) to be deposited per gram (or cc) of thyroid (e.g., activity (μCi) = gland weight (g)×150-200 μCi/g×[1/24 hour uptake in % of administered activity]). The activity in μCi or Bq is converted to mCi or MBq 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

649 compared with anatomic imaging (86); however, other investigators have not confirmed
650 this observation (87).

651 Alternately, a more detailed calculation can be made to deposit a specific
652 radiation dose (in rad or Gy) to the thyroid. Using this approach, it is also necessary to
653 know the effective half-life of RAI (88). This requires additional time and computation
654 and, because the outcome has not shown to be better, this method is seldom used in the
655 United States. Evidence shows that to achieve a hypothyroid state, >150 μCi/g (5.55
656 MBq/g) needs to be delivered (88-90). Patients who are on dialysis or who have
657 jejunostomy or gastric feeding tubes require special care **and management** when being
658 administered RAI treatment (91).

659 The success of RAI therapy in GD strongly depends on the administered
660 activities. In patients without adjunctive ATD, randomized controlled trials found 61%
661 success with 5.4 mCi (200 MBq) (92), 69% with 8.2 mCi (302 MBq) (93), 74% with 10
662 mCi (370 MBq) (94), 81% with 15 mCi (555 MBq) (94) and 86% with 15.7 mCi (580
663 MBq) (95) RAI. Due to the high rate of patients requiring retreatment, RAI therapy with
664 low activities is generally not recommended.

665 A long-term increase in cardiovascular and cerebrovascular deaths has been
666 reported after RAI therapy not resulting in hypothyroidism as opposed to unchanged
667 mortality in RAI-treated patients on levothyroxine therapy, reflecting the role of
668 persistent hyperthyroidism as opposed to that of RAI therapy on mortality (96,97). A
669 recent meta-analysis found no increase in the overall cancer risk after RAI treatment for
670 hyperthyroidism; however, a trend towards increased risk of thyroid, stomach and kidney

cancer was seen, requiring further research (98). In some men, there is a modest fall in the testosterone to luteinizing hormone (LH) ratio after RAI therapy that is subclinical and reversible (99). Conception should be delayed in women **until** stable euthyroidism **is established** (on thyroid hormone replacement following successful thyroid ablation). **This typically takes 4-6 months or longer. Conception should be delayed** 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 (100).

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 RAI after the 10^{th} to 11^{th} week of gestation may be born athyreotic (101,102) and are also at a theoretical increased risk for reduced intelligence and/or cancer. In breast-feeding women, RAI therapy should not be administered for at least 6 weeks after lactation stops to ensure that RAI will no longer be actively concentrated in the breast tissues. A delay of 3 months will more reliably ensure that lactation-associated increase in breast sodium iodide symporter activity has returned to normal (103). Breast feeding should not be resumed after RAI therapy.

■ RECOMMENDATION 10

The physician administering RAI should provide written advice concerning radiation safety precautions following treatment. If the precautions cannot be followed,

alternative therapy should be selected. **Strong recommendation, low-quality evidence.**

All national and regional radiation protection rules regarding RAI treatment should be followed (104,105). 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 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 RAI therapy for GD

■ **RECOMMENDATION 11**

Follow-up within the first 1–2 months after RAI therapy for GD should include an assessment of free T_4, total T_3, and TSH. Biochemical monitoring should be continued at 4–6 week intervals for 6 months, or until the patient becomes hypothyroid and is stable on thyroid hormone replacement. **Strong recommendation, low-quality evidence.**

Most patients respond to RAI therapy with a normalization of thyroid function tests and improvement of clinical symptoms within 4–8 weeks. Hypothyroidism may

occur from 4 weeks on, with 40% of patients being hypothyroid by 8 weeks and >80% by 16 weeks (106). This transition can occur rapidly 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 RAI therapy can rarely occur, with subsequent complete recovery of thyroid function or recurrent hyperthyroidism (107). In such patients the thyroid gland often remains palpable.

Beta-blockers that were instituted prior to RAI treatment should be tapered when free T_4 and total T_3 have returned to the reference range. As free T_4 and total T_3 improve, MMI can usually be tapered, which allows an assessment of the response to RAI.

Most patients eventually develop hypothyroidism following RAI, which is indicated by a free T_4 below normal range. At this point, levothyroxine should be instituted. TSH levels may not rise immediately with the development of hypothyroidism, and should not be used initially to determine the need for levothyroxine. 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 U2). Once euthyroidism is achieved, lifelong annual thyroid function testing is recommended **at least annually, or if the patietn experiences symptoms of hypothyroidism or hyperthyroidism.**

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 total T_3.

[D4] Treatment of persistent Graves' hyperthyroidism following RAI therapy

■ **RECOMMENDATION 12**

When hyperthyroidism due to GD persists after 6 months following RAI therapy, retreatment with RAI is suggested. In selected patients with minimal response 3 months after therapy additional RAI may be considered. **Weak recommendation, low-quality evidence.**

Technical remarks: Response to RAI therapy 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 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 RAI, surgery should be considered (108).

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

ATDs have been employed for seven decades (109). 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 (110). The treatment itself might have a beneficial immunosuppressive role, either to primarily decrease thyroid specific autoimmunity, or secondarily, by ameliorating the hyperthyroid state, which may restore the dysregulated immune system back to normal (111). In fact, the rate of remission with ATD therapy is much higher (112) than the historical rates of spontaneous remission (113).

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

■ **RECOMMENDATION 13**

Methimazole should be used in virtually every patient who chooses ATD therapy for GD, except during the first trimester of pregnancy when propylthiouracil (PTU) is preferred, in the treatment of thyroid storm, and in patients with minor reactions to MMI who refuse radioactive iodine therapy or surgery. **Strong recommendation, moderate-quality evidence.**

■ **RECOMMENDATION 14**

Patients should be informed of side effects of ATDs 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. Preferably, this should be in writing. Before starting ATDs 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. **Strong recommendation, low-quality evidence.**

■ RECOMMENDATION 15

Prior to initiating ATD 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. **Weak recomendation, low-quality evidence.**

In the United States, MMI and PTU are available, and in some countries, carbimazole, a precursor of MMI, is widely used. Carbimazole is rapidly converted to MMI in the serum (10 mg of carbimazole is metabolized to approximately 6 mg of MMI). They work in an identical fashion and both will be referred to as MMI in this text. Both are effective as a single daily dose. At the start of MMI therapy, initial doses of 10–30 mg daily are used to to restore euthyroidism, and then the dose can be titrated down to a maintenance level (generally 5–10 mg daily) (109,114). The dose of MMI should be targeted to the degree of thyroid dysfunction, as too low a dose will not restore a euthyroid state in patients with severe disease (115), and an excessive dose can cause iatrogenic hypothyroidism in patients with mild disease (116). In addition, adverse drug reactions are more frequent with higher MMI doses. Thus, it is important to use an MMI dose that will achieve the clinical goal of normalization of thyroid function reasonably rapidly, while minimizing adverse drug effects. **The task force suggests the following as a** rough guide to initial MMI daily dosing: 5-10 mg if free T_4 is 1-1.5 times the upper limit of normal (ULN); 10-20 mg for free T_4 1.5-2 times the ULN; 30-40 mg for free T_4

796 2-3 times the ULN. These rough guidelines should be tailored to the individual patient,
797 incorporating additional information on symptoms, gland size and total T_3 levels where
798 relevant. Serum T_3 levels are important to monitor initially, as some patients normalize
799 their free T_4 levels with MMI but have persistently elevated serum T_3, indicating
800 continuing thyrotoxicosis (117).

801

802 MMI has the benefit of once-a-day administration and a reduced risk of major
803 side effects compared to PTU. PTU has a shorter duration of action and is usually
804 administered two or three times daily, starting with 50–150 mg three times daily,
805 depending on the severity of the hyperthyroidism. As the clinical findings and thyroid
806 function tests return to normal, reduction to a maintenance PTU dose of 50 mg two or
807 three times daily is usually possible. When more rapid biochemical control is needed in
808 patients with severe thyrotoxicosis, an initial split dose of MMI (e.g., 15 or 20 mg twice a
809 day) may be more effective than a single daily dose, as the duration of action of MMI
810 may be less than 24 hours (118) . Higher doses of antithyroid medication are sometimes
811 administered continuously and combined with L-thyroxine in doses to maintain euthyroid
812 levels (so-called block and replace therapy). However, this approach is not generally
813 recommended, as it has been shown to result in a higher rate of ATD side effects
814 (109,119).

815 The use of potassium iodine (KI) as a beneficial adjunct to ATD therapy for
816 Graves' disease has been investigated in previous studies (120). Indeed, a recent RCT
817 described the administration of 38 mg of potassium iodide (KI) together with 15 mg of

MMI daily, which resulted in better control of hyperthyroidism and fewer adverse reactions compared to 30 mg of MMI given alone (121).

[E2] Adverse effects of Antithyroid Drugs

In general, adverse effects of ATDs can be divided into common, minor allergic side effects and rare but serious allergic/toxic events such as agranulocytosis, vasculitis, or hepatic damage. In a recent systematic review of eight studies that included 667 GD patients receiving MMI or PTU, 13% of patients experienced adverse events (122). The minor allergic reactions included pruritus or a limited, minor rash, in 6% of patients taking MMI and 3% of patients taking PTU (122). **Hepatocellular injury** occurred in 2.7% of patients taking PTU and 0.4% of patients taking MMI. In a separate study of 449 GD patients receiving MMI or PTU, 24% developed a cutaneous reaction, 3.8% developed transaminase elevations more than 3-fold above normal, and 0.7% developed agranulocytosis (absolute neutrophil count (ANC) < 500) (123). Cutaneous reactions were more common with PTU or higher dose MMI (30 mg/day), compared to lower dose MMI (15 mg per day). Hepatotoxicity was more common with PTU. Cutaneous reactions appeared after a median of 18-22 days of treatment, significantly earlier than transaminase elevations (median 28 days). The percentage of patients discontinuing ATD therapy was 17% in the low dose MMI group, 29% in the high dose MMI group, and 34% in the PTU group (123).

[E3] Agranulocytosis

Although ATD associated agranulocytosis is uncommon, it is life-threatening. PTU **at any dose** appears to be more likely to cause agranulocytosis, compared to low doses of MMI (124-126). Three recent reports of large numbers of ATD-treated patients who developed hematologic complications provide information on risk factors, treatment, and outcomes (127-129). Two studies were from Japan and one was from Denmark. In both countries the majority of patients are treated with MMI, so data are more limited for PTU-associated agranulocytosis. In the first study, a retrospective cohort analysis of over 50,000 GD patients, 55 developed agranulocytosis, of whom 5 had pancytopenia, for an estimated cumulative incidence of 0.3% in 100 days (127), with a median interval to onset of 69 days. All 50 patients with agranulocytosis alone were successfully treated with granulocyte colony stimulating factor (G-CSF), steroids, or supportive care, but one of five patients with pancytopenia died. No predictive risk factors for the development of agranulocytosis could be identified. The second study was based on a national database for adverse drug reactions, which may have included some patients reported in the first study (128). Seven-hundred-fifty-four GD patients who developed ATD-induced hematologic complications were reported, for an estimated incidence of 0.1 – 0.15%. Of them, 725 patients received MMI, 28 received PTU, and one received both drugs. Eighty-nine percent developed agranulocytosis and 11% developed pancytopenia or aplastic anemia. At the onset of agranulocytosis, the average MMI dose was 25 mg/day and the average PTU dose was 217 mg/day. The average age of patients developing agranulocytosis was slightly older (45 vs 40 years), an observation that has been made by others. Seventy-two percent developed agranulocytosis within 60 days of starting ATD, and 85% within 90 days. In 7% of patients, agranulocytosis occured later than 4 months

after starting ATD, but some of these patients had discontinued the medication for long periods of time and developed agranulocytosis after a second or subsequent exposure. Thirty of the events (4%) were fatal. In the third study from Denmark, the frequency of agranulocytosis was 0.27% with PTU and 0.11% with MMI (129). As in prior studies, the median duration of therapy prior to the development of agranulocytosis was 36 and 38 days for MMI and PTU, respectively.

[E4] Hepatotoxicity

Hepatotoxicity is another major adverse effect of ATD therapy. MMI hepatotoxicity has been described as typically cholestatic, but hepatocellular disease may be seen (130,131). In contrast, PTU can cause fulminant hepatic necrosis that may be fatal; liver transplantation has been necessary in some patients taking PTU (132). It is for this reason that **in 2010** the FDA issued a safety alert regarding the use of PTU, and an analysis of FDA Medwatch data (133) concluded that children are more susceptible to hepatotoxic reactions from PTU than are adults.

A recent pharmacoepidemiologic study from Taiwan challenges the concept that MMI hepatotoxicity is usually cholestatic, while PTU hepatotoxicity is most often hepatocellular (134). **Among 71,379 new users of ATDs with a median follow-up of 196 days, MMI was associated with a higher rate of a diagnosis of non-infectious hepatitis than PTU (0.25% versus 0.08%, respectively), whereas cholestasis was not different (0.019% versus 0.016%). A diagnosis of liver failure was more common after PTU (0.048% versus 0.026% in MMI treated patients).** Similar findings were also recently reported from China (135). These surprising results from Asia, which are in

contrast to other data from the U.S. (133,136), suggest that prior data on MMI-related hepatotoxicity from small case series may need to be reconsidered. In the study from Denmark (129), hepatotoxic reactions were not classified as cholestatic or hepatocellular, but the frequency of "liver failure" was similar for MMI (0.03%) and PTU (0.03%).

[E5] Vasculitis

Aside from hematologic and hepatic adverse effects, there are other rare side effects with ATDs. PTU, and rarely MMI can cause causes antineutrophil cytoplasmic antibody (pANCA)-positive small vessel vasculitis (137,138) as well as drug induced lupus (139). The risk appears to increase with duration of therapy as opposed to other adverse effects seen with ATDs that typically occur early in the course of treatment (140,141). Typically, granulocyte myeloperoxidase is the targeted antigen of the ANCA, but antibodies to many other proteins are seen as well (142). ANCA positive vasculitis is more common in patients of Asian ethnicity, and the majority of reports come from that part of the world (143). While up to 40% of patients taking PTU develop ANCA positivity, the vast majority of such individuals do not develop clinical vascutitis (144). When the drug is discontinued, the ANCA slowly disappear in most individuals (144). Children seem to be more likely to develop PTU-related ANCA positive vasculitis (133). In most cases, the vasculitis resolves with drug discontinuation, although immunosuppressive therapy may be necessary (145).

Rare cases of insulin autoimmune syndrome with symptomatic hypoglycemia have been reported in patients treated with MMI (146,147).

Technical remarks: Baseline blood tests to aid in the interpretation of future laboratory values should be considered before initiating ATD therapy. This is suggested in part because low white cell counts are common in patients with GD and in African Americans (10% of whom have a neutrophil count under 2000 (148)), and abnormal liver enzymes are frequently seen in patients with thyrotoxicosis (149). **While there is no evidence that neutropenia or liver disease increases the risk of complications from ATDs, the opinion of the task force is that a** baseline absolute neutrophil count $<1000/mm^3$ or liver transaminase enzyme levels elevated more than fivefold above the upper limit of normal should prompt serious reconsideration of initiating ATD 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 online (150,151).

[E6] 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 and total T_3 should be obtained about 2 to 6 weeks after initiation of therapy, depending on the severity of the thyrotoxicosis, and the dose of medication adjusted accordingly. Serum T_3 should be monitored because the serum free T_4 levels may normalize despite persistent elevation of serum total T_3. Serum TSH may

remain suppressed for several months after starting therapy and is therefore not a good parameter for monitoring therapy early in the course.

Once the patient is euthyroid, the dose of MMI can usually be decreased by 30-50%, and biochemical testing repeated in 4-6 weeks. Once euthyroid levels are achieved with the minimal dose of medication, clinical and laboratory evaluation can be undertaken at intervals of 2–3 months. If a patient is receiving long-term MMI (> 18 months), this interval can be increased to 6 months (see below).

■ **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. **Strong recommendation, low-quality evidence.**

■ **RECOMMENDATION 17**

There is insufficient evidence to recommend for or against routine monitoring of white blood cell counts in patients taking ATD's. **No recommendation, insufficient evidence to assess benefits and risks.**

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 (152). 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 is usually sudden in onset. In a recent analysis of 211

patients with ATD-induced agranulocytosis who had at least one prior granulocyte count measured, 21% had a normal white blood count within a week, and 53% within two weeks, before developing agranulocytosis (128). However, other patients did display a gradual decline in white blood cell count prior to developing agranulocytosis, suggesting that monitoring might have been useful in some affected patients (152). 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. If monitoring is employed, the maximum benefit would be for the first 90 days of therapy, when the vast majority of agranulocytosis occurs. In a patient developing agranulocytosis or other serious side effects while taking either MMI or PTU, use of the other medication is contraindicated owing to risk of cross-reactivity between the two medications (153). The contraindication to use PTU might be reconsidered in life-threatening thyrotoxicosis (i.e., thyroid storm) in a MMI-treated patient who has developed agranulocytosis, especially if the duration of therapy is brief (154).

■ **RECOMMENDATION 18**

Liver function and hepatocellular integrity should be assessed in patients taking MMI or PTU who experience pruritic rash, jaundice, light-colored stool or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea, or fatigue. **Strong recommendation, low-quality evidence.**

Hyperthyroidism can itself cause mildly abnormal liver function tests in up to 30% of patients (149). PTU itself 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 (155), 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. A 2009 review of the literature (136) found that PTU hepatotoxicity occurred after a median of 120 days after initiation 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 (156), as the origin of the alkaline phosphatase is from bone, not liver. 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 (115,157-159). Routine monitoring of liver function in all patients taking ATDs has not been found to prevent severe hepatotoxicity. If monitoring is employed, the maximum benefit would be for the first 120 days of therapy, when the vast majority of instances of hepatotoxicity occur.

Technical remarks: PTU should be discontinued if transaminase levels (found incidentally or measured as clinically indicated) reach >3 times the upper limit of normal **or if levels elevated at the onset of therapy increase further.** 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 for specialty care is warranted. Except in cases of severe PTU-induced hepatotoxicity, MMI can be used to control the thyrotoxicosis without ill effect (160,161).

■ **RECOMMENDATION 19**

There is insufficient information to recommend for or against routine monitoring of liver function tests in patients taking ATD's**. No recommendation, insufficient evidence to assess benefits and risks.**

[E7] Management of allergic reactions

■ **RECOMMENDATION 20**

Minor cutaneous reactions may be managed with concurrent antihistamine therapy without stopping the ATD. Persistent **symptomatic** minor side effects of antithyroid medication should be managed by cessation of the medication and changing to RAI or surgery, or switching to the other ATD when RAI or surgery are not options. In the case of a serious allergic reaction, prescribing the alternative drug is not recommended. **Strong recommendation, low-quality evidence.**

A recent study provided evidence that switching from one ATD to the other is safe in the case of minor side effects, although patients may develop similar side effects with the second ATD (123). In this study, 71 patients with an adverse event from either MMI or PTU switched to the other ATD, with doses individually determined. Median dose of the second ATD was 15 mg/d for MMI (range 10 – 30) and 300 mg/day for PTU (range 150 – 450). Thirty-four percent of patients switched to PTU and 30% of patients switched to MMI developed side effects, generally the same type as occurred on the

original ATD, while the remaining patients tolerated the second ATD without complications (123). There is also one recent case report of a more severe reaction to MMI consisting of rash, pruritis, tongue and throat swelling that was successfully managed with antihistamine therapy, but this is not generally recommended due to the risk of analphylaxis (162).

[E8] Duration of antithyroid drug therapy for GD

■ **RECOMMENDATION 21**

Measurement of TRAb levels prior to stopping ATD therapy is suggested, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating greater chance for remission. **Strong recommendation, moderate-quality evidence.**

■ **RECOMMENDATION 22**

If MMI is chosen as the primary therapy for GD, the medication should be continued for approximately 12–18 months, then discontinued if the TSH and TRAb levels are normal at that time. **Strong recommendation, high-quality evidence.**

■ **RECOMMENDATION 23**

If a patient with GD becomes hyperthyroid after completing a course of MMI, consideration should be given to treatment with RAI or thyroidectomy. Continued low-dose MMI treatment for longer than 12–18 months may be considered in patients

not in remission who prefer this approach. **Weak recommendation, low-quality evidence.**

A patient is considered to be in remission if they have had a normal serum TSH, free T_4, and total T_3 for 1 year after discontinuation of ATD therapy. The remission rate varies considerably between geographical areas. In earlier studies in the United States, about 20%–30% of patients were reported to have a lasting remission after 12–18 months of medication, (59), but more recent data are not available. The remission rate may be higher in Europe and Japan; a long-term European study indicated a 50–60% remission rate after 5–6 years of treatment (163), and a study in Japan reported a 68% remission rate after 2 years of treatment (164). A meta-analysis shows the remission rate in adults is not improved by a course of ATDs longer than 18 months (119). A lower remission rate has been described in men, smokers (especially men), and those with large goiters (≥ 80 g) (165-169). Higher initial doses of MMI (60-80 mg/day) do not improve remission rates, but increase the risk of side effects, and are not recommended (170).

TRAb assessment at the end of the course of ATD therapy is a useful method of dividing patients into 2 groups: one with persistent elevations who are unlikely to be in remission, and another group with low or undetectable TRAb, who have a higher probability of permanent remission (171,172). In the group with elevated TRAb, relapse rates approach 80-100%, while in the latter group, relapse rates are in the 20-30% range (171,172).

[E9] Persistently elevated TRAb

Patients with persistently high TRAb could continue ATD therapy **(and repeat TRAb after** an additional 12-18 months) or opt for alternate definitive therapy with RAI or surgery. In selected patients (i.e., younger patients with mild stable disease on a low dose of MMI), long-term MMI is a reasonable alternative approach (65,173). Another study by the same author reported that MMI doses of 2.5 – 10 mg/day for a mean of 14 years were safe and effective for the control of GD in 59 patients (174). A recent retrospective analysis compared long term outcomes (mean follow up period of 6-7 years) of patients who had relapsed after a course of ATDs, who were treated with either RAI and levothyroxine or long-term ATD therapy (175). Those patients treated with RAI (n=114) more often had persistent thyroid eye disease, continuing thyroid dysfunction, and experienced more weight gain compared to those patients receiving long-term ATD treatment (n=124).

If continued MMI therapy is chosen, TRAb levels might be monitored every 1-2 years, with consideration of MMI discontinuation if TRAb levels become negative over long term follow up. For patients choosing long-term MMI therapy, monitoring of thyroid function every 4-6 months is reasonable, and patients can be seen for follow up visits every 6-12 months.

[E10] Negative TRAb

If TRAb is negative **and thyroid function is normal** at the end of 12-18 months of MMI therapy, it is reasonable to discontinue the drug. If a patient experiences a relapse in follow up, RAI therapy or surgery should be considered.

Technical remarks: In patients with negative TRAb, relapses tend to occur relatively later than those that develop in patients whose MMI is stopped when TRAb is still positive (171,176), although 5% occurred within the first 2 months (167). Therefore, in this population, thyroid function testing should be monitored at 2 to 3-month intervals for the first 6 months, then at 4 to 6-month intervals for the next 6 months, then every 6 to 12 months, in order to detect relapses as early as possible. The patient should be counseled to contact the treating physician if symptoms of hyperthyroidism are recognized. Should a relapse occur, patients should be counseled about alternatives for therapy, which would include another course of MMI, RAI, or surgery. If ATD therapy is chosen, patients should be aware that agranulocytosis can occur with a second exposure to a drug, even many years later, despite an earlier uneventful course of therapy (177,178). If the patient remains euthyroid for more than 1 year (i.e., they are in remission), thyroid function should be monitored at least annually, as relapses can occur years later (171), and some patients eventually become hypothyroid (179).

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

[F1] Preparation of patients with GD for thyroidectomy

■ **RECOMMENDATION 24**

If surgery is chosen as treatment for GD, patients should be rendered euthyroid prior to the procedure with ATD pretreatment, with or without beta-adrenergic blockade. A

potassium iodide **containing preparation** should be given in the immediate preoperative period. **Strong recommendation, low-quality evidence.**

■ **RECOMMENDATION 25**

Calcium and 25-OH-vitamin D should be assessed preoperatively and repleted if necessary, or given prophylactically. Calcitriol supplementation should be considered preoperatively in patients at increased risk for transient or permanent hypoparathyroidism. **Strong recommendation, low-quality evidence.**

■ **RECOMMENDATION 26**

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 ATDs, the patient should be adequately treated with beta-blockade, potassium iodide, glucocorticoids, and potentially cholestyramine in the immediate preoperative period. The surgeon and anesthesiologist should have experience in this situation. **Strong recommendation, low-quality evidence.**

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 (180). Preoperative potassium iodide, saturated solution of potassium iodide (SSKI), or Lugol's solution 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 (181,182). In a recent

1111 series of 162 patients with GD and 102 patients with TMNG, none of whom received
1112 SSKI preoperatively, there were no significant differences in operative times, blood loss,
1113 or postoperative complications between the two groups; the authors concluded that
1114 omitting preoperative SSKI for GD patients does not impair patient outcomes (183).
1115 Given that this study was performed at a single high-volume institution, its findings may
1116 not be generalizable; comparison was made between two different pathologies, and there
1117 was no comparison group of patients with GD who received SSKI. It is unclear also
1118 whether it was adequately powered to detect a significant difference, if one existed.
1119 However this study mitigates concern when thyroidectomy is scheduled and SSKI is not
1120 given because of shortages, scheduling issues, patient allergy or patient intolerance. In
1121 addition, rapid preparation for emergent surgery can be facilitated by the use of
1122 corticosteroids (184), and potentially cholestyramine (185-187).

1123 *Technical remarks:* Potassium iodide can be given as 5–7 drops (0.25–0.35 mL)
1124 of Lugol's solution (8 mg iodide/drop) or 1–2 drops (0.05–0.1 mL) of SSKI (50 mg
1125 iodide/drop) three times daily mixed in water or juice for 10 days before surgery.

1126 Recent data suggest that supplementing oral calcium and/or vitamin D
1127 preoperatively may reduce the risk of postoperative hypocalcemia due to parathyroid
1128 injury or increased bone turnover (188). Oltmann et al compared 45 Graves' patients
1129 treated with 1 g oral calcium carbonate three times a day for two weeks prior to surgery
1130 to 38 Graves' patients who underwent thyroidectomy without treatment, as well as 38
1131 euthyroid controls; rates of biochemical and symptomatic hypocalcemia were
1132 significantly higher in non-treated Graves' patients compared to the two other treatment

groups (189). Another study that focused on postoperative hypocalcemia after thyroid surgery for thyroid cancer, not hyperthyroidism, identified a reduction in postoperative symptomatic hypocalcemia when patients have preoperative serum 25-hydroxy vitamin D levels >20 ng/ml (>8 nmol/l) prior to the operating room (190). A meta-analysis of risk factors for postoperative hypocalcemia identified preoperative vitamin D deficiency as a risk factor for postoperative hypocalcemia, as well as GD itself (188). In two studies included in another meta-analysis, supplementing calcitriol for a brief period preoperatively helped reduce transient post-thyroidectomy hypocalcemia (191-193).

[F2] The surgical procedure and choice of surgeon

■ **RECOMMENDATION 27**

If surgery is chosen as the primary therapy for GD, near-total or total thyroidectomy is the procedure of choice. **Strong recommendation, moderate-quality evidence.**

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 (194-197). The most common complications following near-total or total thyroidectomy are hypocalcemia due to hypoparathyroidism (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 28**

If surgery is chosen as the primary therapy for GD, the patient should be referred to a high-volume thyroid surgeon. **Strong recommendation, moderate-quality evidence.**

Improved patient outcome has been shown to be independently associated with high thyroidectomy surgeon volume; specifically, average complication rates, 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 (198,199). Data show that surgeons who perform more than 25 thyroid surgeries per year have superior patient clinical and economic outcomes compared to those who perform fewer; **complication rates are 51% higher on average when surgery is performed by low-volume surgeons** (62,199,200). 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. Following thyroidectomy for GD in the hands of high-volume thyroid surgeons, the rate of permanent hypoparathyroidism has been determined to be <2%, and permanent recurrent laryngeal nerve (RLN) injury occurs in <1% (201). The frequency of bleeding necessitating reoperation is 0.3%–0.7% (202). Mortality following thyroidectomy is between 1 in 10,000 and 5 in 1,000,000 (203).

[F3] Postoperative care

■ **RECOMMENDATION 29**

Following thyroidectomy for GD, alternative strategies may be undertaken for management of calcium levels: serum calcium ± intact parathyroid hormone levels can be measured, and oral calcium and calcitriol supplementation administered based on these results, or prophylactic calcium with or without calcitriol prescribed empirically. **Weak recommendation, low-quality evidence.**

Successful prediction of calcium status after total thyroidectomy can be achieved using the slope of 6- and 12-hour postoperative calcium levels (204-210). Postoperative routine supplementation with oral calcium and calcitriol decreases development of hypocalcemic symptoms and intravenous calcium requirement, allowing for safer early discharge (211). 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 (212,213). However, normal levels of serum iPTH may not predict eucalcemia for GD patients (214). Vitamin D insufficiency may serve as an underlying cause.

Patients can be discharged if they are asymptomatic and their serum calcium levels corrected for albumin are 8.0 mg/dL (2.0 mmol/L) or above and are not falling over a 24-hr period. The use of ionized calcium measurements are preferred by some, and are helpful if the patient has abnormal levels of serum proteins. 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. In patients with severe hypocalcemia,

teriparatide administration has yielded encouraging preliminary results (elimination of symptoms and earlier hospital discharge), but more data are needed before it can be considered for clinical practice (215). Persistent hypocalcemia in the postoperative period should prompt measurement of serum magnesium and possible magnesium repletion (216,217). In addition to reduced serum calcium levels, reduced serum phosphate and increased serum potassium levels may be observed in hungry bone syndrome. 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. As the patient reaches eucalcemia, calcium and calcitriol therapy can be tapered.

Technical remarks: Calcium supplementation can be accomplished with oral calcium (usually calcium carbonate, 1250–2500 mg, equivalent to 500-1000 mg elemental calcium) four times daily, tapered by 500 mg of elemental calcium 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 (218) 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 discharge with continuation of supplementation based on clinical parameters.

■ **RECOMMENDATION 30**

ATD should be stopped at the time of thyroidectomy for GD, and beta-adrenergic blockers should be weaned following surgery. **Strong recommendation, low-quality evidence.**

■ **RECOMMENDATION 31**

Following thyroidectomy for GD, L-thyroxine should be started at a daily dose appropriate for the patient's weight (0.8 μg/lb or 1.6 μg/kg), with elderly patients needing somewhat less, and serum TSH measured 6–8 weeks postoperatively. **Strong recommendation, low-quality evidence.**

Technical remarks: **If TSH was suppressed preoperatively, a free T_4 and TSH should be measured 6-8 weeks postoperatively, since recovery of the pituitary-thyroid axis is occasionally delayed.** The appropriate dosing of L-thyroxine will vary with patient BMI (219), and the percent of levothyroxine absorbed from the gut. Once stable and normal, TSH should be measured annually or more frequently if clinically indicated.

■ **RECOMMENDATION 32**

Communication among different members of the multidisciplinary team is essential, particularly during transitions of care in the pre- and postoperative settings. **Strong recommendation, low-quality evidence.**

It is important to assure that adequate communication occurs between the medical team and the treating surgeon to assure that euthyroidism is achievable prior to surgical

intervention; in addition, if the patient is noted to have significant vitamin D deficiency, preoperative vitamin D repletion could be performed and surgery scheduled to permit this. Important intraoperative findings and details of postoperative care, including calcium supplementation needs and management of surgical hypothyroidism, should be communicated by the surgeon to the patient and the other physicians who will be important in the patient's postoperative care (220).

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

■ **RECOMMENDATION 33**

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. **Strong recommendation, moderate-quality evidence.**

Thyroid cancer occurs in GD with a frequency of 2% or less (221). Thyroid nodules larger than 1–1.5 cm should be evaluated before RAI therapy. If a radioactive iodine scan is performed, any nonfunctioning or hypo-functioning nodules should be considered for fine needle aspiration (FNA), as these may have a higher probability of being malignant (62). If the cytopathology is suspicious or diagnostic of malignancy, surgery is advised after normalization of thyroid function with ATDs. Surgery should also be considered for indeterminate cytology. Disease-free survival at 20 years is reported to be 99% after thyroidectomy for GD in patients with small (≤1 cm) coexisting thyroid cancers (222).

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 (which may lead to surgery) can be recommended (223,224).

Technical remarks: The ATA recently published updated management guidelines for patients with thyroid nodules and differentiated thyroid cancer (225).

[H] How should thyroid storm be managed?

■ **RECOMMENDATION 34**

The diagnosis of thyroid storm should be made clinically in a severely thyrotoxic patient with evidence of systemic decompensation. Adjunctive use of a sensitive diagnostic system should be considered. Patients with a Burch-Wartofsky Point Scale (BWPS) of ≥ 45 or Japanese Thyroid Association (JTA) categories of TS1 or TS2 with evidence of systemic decompensation require aggressive therapy. The decision to use aggressive therapy in patients with a BWPS of 25-44 should be based on clinical judgment. **Strong recommendation, moderate-quality evidence.**

■ **RECOMMENDATION 35**

A multimodality treatment approach to patients with thyroid storm should be used, including beta-adrenergic blockade, antithyroid drug therapy, inorganic iodide,

corticosteroid therapy, cooling with acetaminophen and cooling blankets, volume resuscitation, nutritional support, respiratory care and monitoring in an intensive care unit, as appropriate for an individual patient. **Strong recommendation, low-quality evidence.**

Life-threatening thyrotoxicosis or thyroid storm is a rare disorder characterized by multisystem involvement and mortality rates in the range of 8-25% in modern series (25,72,226,227). A high index of suspicion for thyroid storm should be maintained in patients with thyrotoxicosis associated with any evidence of systemic decompensation. Diagnostic criteria for thyroid storm in patients with severe thyrotoxicosis were first proposed in 1993 and subsequently widely adopted as the Burch-Wartofsky Point Scale for thyroid storm (26,72,186,226,228). These criteria (Table 6) include hyperpyrexia, tachycardia, arrhythmias, congestive heart failure, agitation, delirium, psychosis, stupor and coma, as well as nausea, vomiting, diarrhea, hepatic failure, and the presence of an identified precipitant (26). Points are awarded in the BWPS system based on the severity of individual manifestations, with a point total of ≥ 45 consistent with thyroid storm, 25-44 points classified as impending thyroid storm, and < 25 points making thyroid storm unlikely. Recently, an additional empirically defined diagnostic system has been proposed by the Japanese Thyroid Association (JTA) (72). The JTA system uses combinations of similar clinical features to assign patients to the diagnostic categories thyroid storm 1 (TS1) or thyroid storm 2 (TS2).

Data comparing these two diagnostic systems suggest an overall agreement, but a tendency toward under-diagnosis using the JTA categories of TS1 and TS2, compared to

a BWPS ≥ 45 (72,186,226,227). In a recent study including 25 patients with a clinical diagnosis of thyroid storm, the BWPS was ≥ 45 in 20 patients and 25-44 in the remaining five, but these latter five patients (20%) were not identified using the JTA system (226).

Importantly, in the same series, among 125 patients hospitalized with a clinical diagnosis of compensated thyrotoxicosis but not in thyroid storm, 27 (21.6%) had a BWPS ≥ 45, and 21 (16.8%) were either TS1 or TS2, suggesting similar rates of over-diagnosis with these two systems. However, an additional 50 patients (40%) hospitalized with a clinical diagnosis of thyrotoxicosis without thyroid storm would have been diagnosed as having impending thyroid storm by the BWPS, which reinforces that a BWPS in the 25-44 range does not supplant clinical judgment in the selection of patients for aggressive therapy.

In summary, the diagnosis of thyroid storm remains a clinical one that is augmented by current diagnostic systems. A BWPS ≥ 45 appears more sensitive than a JTA classification of TS1 or TS2 in detecting patients with a clinical diagnosis of thyroid storm, but patients with a BWPS of 25-44 represent a group in whom the decision to use aggressive therapy should be based on sound clinical judgment, and not based solely on diagnostic category, in order to avoid over-treatment and the resultant risk of drug toxicity. At a minimum, patients in this intermediate category should be observed closely for deterioration. Care should be taken with either system to avoid inappropriate application to patients without severe thyrotoxicosis as each of the manifestations of thyroid storm, with the possible exception of severe hyperpyrexia, may also be seen in

the presence of any major illness, many of which are also known precipitants of thyroid storm (186).

Precipitants of thyroid storm in a patient with previously compensated thyrotoxicosis include abrupt cessation of ATDs, thyroidectomy, or nonthyroidal surgery in a patient with unrecognized or inadequately treated thyrotoxicosis, and a number of acute illnesses unrelated to thyroid disease (72,186,228). Thyroid storm occasionally occurs following RAI therapy.

Aggressive treatment for thyroid storm involves the early targeting of each pharmacologically accessible step in thyroid hormone production and action (Table 7). Treatment strategy for thyroid storm can be broadly divided into 1) therapy directed against thyroid hormone secretion; 2) measures directed against the peripheral action of thyroid hormone at the tissue level; 3) reversal of systemic decompensation; 4) treatment of the precipitating event or intercurrent illness; and 5) definitive therapy (26). A number of therapeutic measures are specifically intended to decrease T_4-to-T_3 conversion, such as the preferential use of PTU over MMI (229,230), glucocorticoid therapy (231), and the use of beta adrenergic blocking agents such as propranolol, with selective ability to inhibit type 1 deiodinase (232). For example, an early article comparing acute changes in thyroid hormone level after initiation of PTU or MMI found that T_3 levels dropped by approximately 45% in the first 24 hours of PTU therapy compared to an approximately 10-15% decrease after starting MMI (229). Both plasmapheresis/ plasma exchange and emergency surgery have been used to treat thyroid storm in patients who respond poorly to traditional therapeutic measures (233,234).

Prevention of thyroid storm involves recognition and active avoidance of common precipitants, patient education to avoid abrupt discontinuation of ATD therapy, and ensuring that patients are euthyroid prior to elective surgery, labor and delivery, or other acute stressors.

Technical remarks: Treatment with inorganic iodine (SSKI/Lugol's solution), or oral cholecystographic agents (235) leads to rapid decreases in both T_4 and T_3 levels. Combined with ATDs in patients with severe thyrotoxicosis, these agents result in rapid clinical improvement (120). Unfortunately, the oral radiographic contrast agents ipodate and iopanoic acid are not currently available in many countries.

[I] Is there a role for iodine as primary therapy in the treatment of GD?

Prior to the introduction of ATDs, iodine was commonly reported to ameliorate the hyperthyroidism associated with GD (236,237). Iodine acutely lowers thyroid hormone concentrations by reducing hormone secretion (238,239), and inhibits its own organification (the Wolff-Chaikoff effect) (240). However, reports of escape from these beneficial effects of iodine (241), as well as reports of iodine induced hyperthyroidism in patients with nodular goiter (242), discouraged the use of iodine in GD. Recent studies have suggested a potential role for iodine in patients who have had adverse reactions to ATD and who also have a contraindication or aversion to RAI or surgery (243,244).

RECOMMENDATION 36

Potassium iodide may be of benefit in select patients with hyperthyroidism due to GD, who have adverse reactions to ATDs, and have a contraindication or aversion to RAI therapy (or **aversion** to repeat RAI therapy) or surgery. Treatment may be more suitable for patients with mild hyperthyroidism, or a prior history of RAI therapy**. No recommendation, insufficient evidence to assess benefits or risks.**

Among 44 Japanese patients who had adverse reactions to ATD and who were treated with KI alone, 66% were well-controlled for an average of 18 years (range 9-28 years), and 39% achieved a remission after 7 years (range 2-23 years) (243). Among the responders, the doses used were between 13 and 100 mg, and were adjusted depending upon biochemical response. Among 15 nonresponders, 11 (25% of all patients) escaped the inhibitory effects of iodine and 4 patients did not respond at all to KI. None of the patients had side effects. Initial free T_4 concentration and goiter size did not predict a response to therapy. Among 20 Japanese patients with mild hyperthyroidism initially treated with KI alone, and matched using propensity score analysis with patients treated with MMI alone, 85% of the patients treated with KI alone had normal thyroid function at 6 months and 1 year, comparable to that of the matched controls treated with MMI (244). Most patients were treated with 50 mg KI daily.

The inhibitory effects of iodine are greater in patients with a prior history of RAI exposure (245) suggesting a role for KI in patients who remain hyperthyroid after one dose of RAI and prefer to avoid a second dose. The use of KI prior to thyroidectomy for GD is discussed in section [F1], the use of KI as adjunctive therapy following RAI is

discussed in section [D1], the use of KI in combination with MMI for treating GD is discussed in section [E1], and the use of KI in hyperthyroidism complicating pregnancy is discussed in section [T].

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

■ **RECOMMENDATION 37**

We suggest that patients with overtly TMNG or TA be treated with RAI therapy or thyroidectomy. On occasion, long-term, low-dose treatment with MMI may be appropriate. **Weak recommendation, moderate-quality evidence.**

There are two effective and relatively safe definitive treatment options for TMNG and TA, RAI therapy and thyroid surgery. 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 and/total thyroidectomy (246,247), compared with a 20% risk of the need for retreatment following RAI therapy (246,248). Euthyroidism is achieved within days after surgery (246,247). On the other hand, the risk of hypothyroidism and the requirement for exogenous thyroid hormone therapy is 100% after near-total/total thyroidectomy. For patients with TMNG who receive RAI

1404 therapy, the response is 50–60% by 3 months, and 80% by 6 months (246,248,249). In
1405 a large study of patients with TMNG treated with RAI, the prevalence of
1406 hypothyroidism was 3% at 1 year and 64% at 24 years (250). Hypothyroidism was
1407 more common among patients under 50 years of age, compared with those over 70
1408 years (61% vs. 36% after 16 years). In a more recent study, the prevalence of
1409 hypothyroidism was 4% at 1 year and 16% at 5 years (251).

1410 In large retrospective series of patients with TMNG presenting with
1411 compressive symptoms, all patients undergoing total thyroidectomy had resolution of
1412 these symptoms after treatment, whereas only 46% of patients undergoing RAI had
1413 improvement in such symptoms (252). This may be due in part to the fact that very
1414 large goiters treated with high-activity radioactive iodine only decrease in size by 30%–
1415 50% (253).

1416 For patients with TA, the risk of treatment failure is <1% after surgical resection
1417 (ipsilateral thyroid lobectomy or isthmusectomy) (254). Typically, euthyroidism is
1418 achieved within days after surgery. The prevalence of hypothyroidism varies from 2-
1419 3% following lobectomy for TA, although rates of hypothyroidism after lobectomy for
1420 non-toxic nodules have been reported to be as high as 20% (254-256), and lower after
1421 isthmusectomy in the unique circumstance where the TA is confined to the thyroid
1422 isthmus. For patients with TA who receive RAI therapy there is a 6%–18% risk of
1423 persistent hyperthyroidism and a 3%- 5.5% risk of recurrent hyperthyroidism
1424 (254,257). There is a 75% response rate by 3 months and 89% rate by 1 year following
1425 RAI therapy for TA (225,257,258). The prevalence of hypothyroidism after RAI is

progressive and hastened by the presence of antithyroid antibodies or a nonsuppressed TSH at the time of treatment (257,259,260). A study following 684 patients with TA treated with RAI reported a progressive increase in overt and subclinical hypothyroidism (259). 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. The nodule is rarely eradicated in patients with TA undergoing RAI therapy, which can lead to the need for continued surveillance (225,257,260).

Potential complications following near-total/total thyroidectomy include the risk of permanent hypoparathyroidism (<2.0%) or RLN injury (<2.0%) (261,262). There is a small risk of permanent RLN injury with surgery for TA (254). Following RAI therapy, there have been reports of new-onset GD (up to 4% prevalence) (263), as well as concern for thyroid malignancy (254,264,265) and a very minimal increase in late non-thyroid malignancy (265). Overall, the success rate of RAI (definitive hypothyroidism or euthyroidism) is high: 93.7% in TA and 81.1% in TMNG patients (266).

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. Autonomy is an uncommon cause of hyperthyroidism in pregnancy and there is a lack of studies in this setting. However, considering the theoretical risks associated with surgery or ATD therapy (has to be used throughout pregnancy and there is a tendency to overtreat the fetus), the optimal therapy might be definitive therapy with RAI or surgery in advance of a planned pregnancy. Most experts prefer to avoid the use of RAI within 6 months of a pregnancy; it should be used with caution if at all.

The panel agreed that TMNG and TA with high nodular RAI uptake and widely suppressed RAI uptake in the perinodular thyroid tissue are especially suitable for RAI therapy. However, there are insufficient data to make a recommendation based on these findings.

Factors that favor a particular modality as treatment for TMNG or TA (Table 8):

a. RAI therapy: 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 (252).

c. ATDs: Advanced age, comorbities with increased surgical risk or associated with decreased life-expectancy, and not good candidates for ablative therapy.

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

a. RAI therapy: Definite contraindications to the use of radioactive iodine include pregnancy, lactation, coexisting thyroid cancer, individuals unable to comply with radiation safety guidelines and used with caution in women 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, **or lack of access to a high volume thyroid surgeon.** Pregnancy is a relative contraindication and should only be used in this circumstance when rapid control of hyperthyroidism is required and ATDs 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) (67,68).
c. Definite contraindications to ATD therapy include previous known major adverse reactions to ATDs.

Factors that may impact patient preference:

a. RAI therapy: Patients with either TMNG or TA choosing RAI 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 RAI treatment.

b. Surgery: Patients choosing surgery would likely place a relatively higher value on definitive control of hyperthyroid symptoms, avoidance of exposure to radioactivity and a lower value on potential surgical and anesthetic risks; patients with TMNG choosing surgery would place a lower value on the certain need for lifelong thyroid hormone replacement whereas patients with TA who choose surgery would place greater value on the possibility of achieving euthyroidism without hormone replacement.

c. ATDs: Patients choosing ATDs would likely place a relatively higher value on avoidance of exposure to radioactivity and on potential surgical and anesthetic risks and a lower value on the certain need for lifelong thyroid ATD therapy.

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

[K1] Preparation of patients with TMNG or TA for RAI therapy.

■ **RECOMMENDATION 38**

Because RAI treatment of TMNG or TA can cause a transient exacerbation of hyperthyroidism, beta-adrenergic blockade should be considered even in asymptomatic patients who are at increased risk for complications due to worsening of hyperthyroidism, i.e. elderly patients and patients with co-morbidities. **Weak recommendation, low-quality evidence.**

Medical management before RAI therapy should be tailored to the **patient's risk for complications if hyperthyroidism worsens**, 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 RAI for either TMNG or nontoxic multindoular goiter (MNG) (267-269). In susceptible patients with pre-existing cardiac disease or in the elderly, this may produce significant clinical worsening (268). 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 (31). The decision regarding the use of MMI pretreatment is more complex and is discussed below.

■ **RECOMMENDATION 39**

In addition to beta-adrenergic blockade (see Recommendation 2 **and 38**) pretreatment with MMI prior to RAI 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. **Weak recommendation, low-quality evidence.**

■ **RECOMMENDATION 40**

In patients who are at increased risk for complications due to worsening of hyperthyroidism, resuming ATDs 3-7 days after RAI administration should be considered. **Weak recommendation, low quality evidence.**

Young and middle-aged patients with TMNG or TA generally do not require pretreatment with ATDs (MMI) before receiving RAI, but may benefit from beta-blockade if symptoms warrant and contraindications do not exist.

Technical remarks: If an ATD is used in preparation for RAI therapy in patients with TMNG or TA, caution should be taken to avoid RAI therapy when the TSH is normal or elevated to prevent direct RAI treatment of perinodular and contralateral normal thyroid tissue, which increases the risk of developing hypothyroidism. However, if volume reduction is a goal, at the expense of an increased risk of hypothyroidism, pretreatment with MMI, allowing the TSH to rise slighty prior to RAI administration, results in greater volume reduction after fixed doses of RAI (270). Similarly, a recent meta-analysis indicated that the application of rhTSH before RAI therapy in non-toxic or TMNG results in greater thyroid volume reduction but higher hypothyroidism rates than RAI therapy alone (271). Unless volume reduction is an important goal, rhTSH administration before RAI therapy of TMNG is not generally recommended as it could

possibly exacerbate hyperthyroidism (272), it represents an off-label use, and mainly stimulates RAI uptake in TSH-sensitive perinodular tissues (273).

[K2] Evaluation of thyroid nodules before RAI therapy

■ **RECOMMENDATION 41**

Nonfunctioning nodules on radionuclide scintigraphy or nodules with suspicious ultrasound characteristics should be managed according to published guidelines regarding thyroid nodules in euthyroid individuals. **Strong recommendation, moderate-quality evidence.**

Thorough assessment of suspicious nodules within a TMNG, according to the published guidelines (225,274), should be completed before selection of RAI as the treatment of choice. The prevalence of thyroid cancer in TMNG historically has been estimated to be about 3% (247). More recently, it has been estimated to be as high as 9%, which is similar to the 10.6% prevalence noted in nontoxic MNG (275).

Technical remarks: Both the ATA and AACE, the latter in conjunction with the European Thyroid Association and Associazione Medici Endocrinologi, and the Latin American Thyroid Society have published management guidelines for patients with thyroid nodules (225,274,276,277).

[K3] Administration of RAI in the treatment of TMNG or TA

■ **RECOMMENDATION 42**

Sufficient activity of RAI should be administered in a single application to alleviate hyperthyroidism in patients with TMNG. **Strong recommendation, moderate-quality evidence.**

The goal of RAI therapy, especially in older patients, is elimination of the hyperthyroid state. Higher activities of RAI, 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 RAI therapy for TMNG, with a higher prevalence among patients who required more than one treatment (250). The prevalence of hypothyroidism following RAI therapy is increased by normalization or elevation of TSH at the time of treatment resulting from ATD pretreatment or use of rhTSH, and by the presence of antithyroid antibodies (278).

The activity of RAI used to treat TMNG, calculated on the basis of goiter size to deliver 150–200 μCi (5.55-7.4 MBq) 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 applied activity of RAI. Radiation safety precautions may be onerous if high activities of RAI are needed for large goiters. Both pretreatment with MMI allowing the TSH to rise slightly (270), or the off-label use of rhTSH (271), may reduce the total activity of RAI needed, but increase the risk of hypothyroidism (see prior discussion section [K1]).

Technical remarks: **Enlargement** of the thyroid is very rare after RAI treatment. However, patients should be advised to immediately report any tightening of the neck,

difficulty breathing, or stridor following the administration of RAI. Any compressive symptoms, such as discomfort, swelling, dysphagia, or hoarseness, which develop following RAI therapy, 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 43**

Sufficient activity of RAI should be administered in a single application to alleviate hyperthyroidism in patients with TA. **Strong recommendation, moderate-quality evidence.**

RAI administered to treat TA can be given either as a fixed activity of approximately 10–20 mCi (370-740 MBq) or an activity calculated on the basis of nodule size using 150–200 μCi (5.5-7.4 MBq) RAI per gram corrected for 24-hour RAIU (278). A long-term follow-up study of patients with TA, where patients with **nodules** <4 cm were administered an average of 13 mCi (481 MBq) and those with larger nodules an average of 17 mCi (629 MBq), showed a progressive increase in hypothyroidism over time in both groups, suggesting that hypothyroidism develops over time regardless of activity adjustment for nodule size (259). A randomized trial of 97 patients with TA compared the effects of high (22.5 mCi / 833 MBq) or low (13 mCi / 481 MBq) fixed activity RAI, with a calculated activity that was either high (180–200 μCi/g / 6.7-7.4 Bq) or low (90–100 μCi/g / 3.3-3.7 Bq) and corrected for 24-hour RAIU (279). This study confirmed previous reports showing an earlier disappearance of hyperthyroidism and

earlier appearance of hypothyroidism with higher RAI activity. Use of a calculated activity allowed for a lower RAI activity to be administered for a similar efficacy in the cure of hyperthyroidism.

[K4] Patient follow-up after RAI therapy for TMNG or TA

■ **RECOMMENDATION 44**

Follow-up within the first 1–2 months after RAI therapy for TMNG or TA should include an assessment of free T_4, total T_3 and TSH. Biochemical monitoring should be continued at 4–6 week intervals for 6 months, or until the patient becomes hypothyroid and is stable on thyroid hormone replacement. **Strong recommendation, low-quality evidence.**

RAI 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% (246-248). Goiter volume is decreased by 3 months, with further reduction observed over 24 months, for a total size reduction of 40% (248). 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 (257). Risk of persistent or recurrent hyperthyroidism ranged from 0% to 30%, depending on the series (246-248,257). 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 (259), and an average of 3% by 1 year and 64% by 24 years for TMNG (250).

Graves' disease might develop after RAI for TMNG in up to 4% of patients (280). Such patients develop worsening hyperthyroidism within a few months of RAI therapy. Treatment with additional RAI is effective.

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

[K5] Treatment of persistent or recurrent hyperthyroidism following RAI therapy for TMNG or TA

■ **RECOMMENDATION 45**

If hyperthyroidism persists beyond 6 months following RAI therapy for TMNG or TA, retreatment with RAI is suggested. In selected patients with minimal response 3 months after therapy additional RAI may be considered. **Weak recommandation, low-quality evidence.**

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

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

[L1] Preparation of patients with TMNG or TA for surgery

■ **RECOMMENDATION 46**

If surgery is chosen as treatment for TMNG or TA, patients with overt hyperthyroidism should be rendered euthyroid prior to the procedure with MMI pretreatment, with or without beta-adrenergic blockade. Preoperative iodine should not be used in this setting. **Strong recommendation, low-quality evidence.**

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 (281,282). The literature reports a very low risk of anesthesia-related mortality associated with thyroidectomy (254,283). Preoperative iodine therapy is not indicated due to the risk of exacerbating the hyperthyroidism (284). Usually hyperthyroidism is less severe in patients with TMNG, so that in most cases, patients with allergy to ATDs can be prepared for surgery, when necessary, with beta-blockers alone.

[L2] The surgical procedure and choice of surgeon

■ **RECOMMENDATION 47**

If surgery is chosen as treatment for TMNG, near-total or total thyroidectomy should be performed. **Strong recommendation, moderate-quality evidence.**

Recurrence can be avoided in TMNG if a near-total or total thyroidectomy is performed initially (285). This procedure can be performed with the same low rate of complications as a subtotal thyroidectomy (286-289). Reoperation for recurrent or persistant goiter results in a 3- to 10-fold increase in the risk of permanent vocal cord paralysis or hypoparathyroidism (290,291).

■ **RECOMMENDATION 48**

Surgery for TMNG should be performed by a high-volume thyroid surgeon. **Strong recommendation, moderate-quality evidence.**

TMNG is more common in older patients. 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 (198). Data showing equivalent outcomes among the elderly usually have come from high-volume centers (292). 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 (198,199,293). The recommendation for referral to a high-volume surgeon is essentially the same as that described in section [F2] for the choice of surgeon in GD.

■ **RECOMMENDATION 49**

If surgery is chosen as the treatment for TA, a thyroid ultrasound should be done to evalutate the entire thyroid gland. An ipsilateral thyroid lobectomy, or isthmusectomy if the adenoma is in the thyroid isthmus, should be performed for isolated TAs. **Strong recommendation, moderate-quality evidence.**

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 (254). In patients who wish to avoid general anesthesia or who have significant comorbidities, the risk of anesthesia can be lowered further when cervical block analgesia with sedation is employed by thyroid surgeons and anesthesiologists experienced in this approach (294). Patients with positive antithyroid antibodies preoperatively have a higher risk of postoperative hypothyroidism (256,278).

■ **RECOMMENDATION 50**

We suggest that surgery for TA be performed by a high-volume surgeon. **Weak recommendation, moderate-quality evidence.**

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 RAI therapy. High-volume thyroid surgeons tend to have better outcomes following

lobectomy than low-volume surgeons, but the differences are not statistically significant (198). High-volume surgeons may be more comfortable with performing the thyroid lobectomy under cervical block analgesia with sedation.

[L3] Postoperative care

■ **RECOMMENDATION 51**

Following thyroidectomy for TMNG, serum calcium ± iPTH levels should be measured, and oral calcium and calcitriol supplementation administered based on the results. **Weak recommendation, low-quality evidence.**

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 risk of postoperative hypocalcemia.

■ **RECOMMENDATION 52**

MMI should be stopped at the time of surgery for TMNG or TA. Beta-adrenergic blockade should be slowly discontinued following surgery. **Strong recomendation, low-quality evidence.**

Technical remarks: **The duration over which beta-adrenergic blockade should be tapered should take into account the preoperative free T_4 concentration, the**

heart rate, and the week-long half-life of T_4. Additionally, patients taking higher doses of beta-blockers will require a longer taper.

■ RECOMMENDATION 53

Following thyroidectomy for TMNG, thyroid hormone replacement should be started at a dose appropriate for the patient's weight (0.8 mcg/lb or 1.6 mcg/kg) and age, with elderly patients needing somewhat less. TSH should be measured every 1–2 months until stable, and then annually. **Strong recommendation, low-quality evidence.**

Technical remarks: The appropriate dosing of L-thyroxine will vary with patient BMI (219). 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 54

Following lobectomy 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. **Strong recommendation, low-quality evidence.**

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.

Thyroid hormone replacement is required in about 15-20% of patients following thyroid lobectomy (295). Serum TSH levels may have been suppressed or normal prior to lobectomy, depending on the degree of preoperative preparation with ATDs. TSH levels may remain in the high normal range for 3-6 months following lobectomy; therefore, continued monitoring in an asymptomatic patient for 4-6 months postoperatively is reasonable, since there may be eventual recovery of normal thyroid function (296).

[L4] Treatment of persistent or recurrent disease following surgery for TMNG or TA

■ **RECOMMENDATION 55**

RAI therapy should be used for retreatment of persistent or recurrent hyperthyroidism following inadequate surgery for TMNG or TA. **Strong recommendation, low-quality evidence.**

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 RAI therapy (290,291). If this is not an option, it is essential that the surgery be performed by a high-volume thyroid surgeon.

[M] If ATDs are chosen as treatment of TMNG or TA, how should the therapy be managed?

ATDs do not induce remission in patients with nodular thyroid disease. Therefore, discontinuation of treatment results in relapse (262,297). However, prolonged (life-long) ATD therapy may be the best choice for some individuals with limited life-expectancy and increased surgical risk, including residents of nursing homes or other care facilities where compliance with radiation safety regulations may be difficult.

■ **RECOMMENDATION 56**

Long-term MMI treatment of TMNG or TA might be indicated in some elderly or otherwise ill patients with limited life-expectancy, in patients who are not good candidates for surgery or ablative therapy, and in patients who prefer this option. **Weak recommendation, low-quality evidence.**

Technical remarks: The required dose of MMI to restore the euthyroid state in TMNG or TA patients is usually low (5-10 mg/day). Because long-term, low-dose ATD treatment in nodular hyperthyroidism can be difficult to regulate, frequent (every 3 months) monitoring is recommended initially, especially in the elderly (298), until stability has been documented after which testing frequency can be decreased.

[N] Is there a role for ethanol or radiofrequency ablation in the management of TA or TMNG?

■ **RECOMMENDATION 57**

Alternative therapies such as ethanol or radiofrequency ablation of TA and TMNG can be considered in select patients where RAI, surgery or long-term ATD are inappropriate, contraindicated, or refused, and expertise in these procedures is available. **No recommendation, insufficient evidence to assess benefits and risks.**

[N1] Ethanol ablation

Reports that support the efficacy of percutaneous ethanol injection (PEI) under sonographic guidance to treat TA and TMNG come largely from Europe (299-301). Experience in the United States is limited. A typical protocol involves the injection of ethanol (average dose 10 ml, depending on size of the area to be ablated) into the TA or autonomous area of a TMNG. In one study, the average patient required 4 sessions at 2 week intervals (299). One hundred twenty-five patients with TA were followed for an average of 5 years; 2.4% refused further treatment due to pain, and 3.2% had complications including transient recurrent laryngeal nerve palsy, abscess or hematoma (299). Ninety-three percent of patients achieved a functional cure (no uptake on RAI scintigraphy), and 92% had a > 50% reduction in nodule size (299). In another study of both TA and TMNG, 78 percent achieved a functional cure, all nodules regressed, and there was no recurrent hyperthyroidism during 5-years of follow-up (300). Ethanol ablation also has been used following RAI to reduce nodule size (301). However, its use has been limited due to pain associated with extravasation of the ethanol to extranodular locations, and other adverse effects which have included transient thyrotoxicosis, permanent ipsilateral facial dysethesia, paranodular fibrosis interfering with subsequent surgery (302), and toxic necrosis of the larynx and adjacent skin (303).

[N2] Radiofrequency ablation

Both radiofrequency ablation (RFA) and laser therapy have been used to treat thyroid nodules. A meta-analysis demonstrated that RFA resulted in larger reductions in nodule size with fewer sessions than laser (304). A retrospective multi-center report of RFA for TA in 44 patients utilized an 18 g electrode under ultrasound guidance with a mean follow-up of 20 months (305). An 82% reduction in nodule volume was achieved, but 20% of nodules remained autonomous on scintigraphy, and 18% of patients remained hyperthyroid. All patients complained of pain during the procedure, but there were no complications (305). A Korean study compared the use of RFA to surgery for non-toxic nodules (306). RFA was associated with an 85% reduction in nodule size, the cost was similar to surgery, there were fewer complications (recurrent laryngeal nerve injury or hypoparathyroidism: 6% for surgery and 1% for RFA), and no patient who received RFA became hypothyroid (306). Advocates of RFA argue that it preserves normal thyroid function compared to surgery or RAI (307). However, additional data are needed to determine the success at correcting hyperthyroidism in patients with TA and TMNG. The use of RFA should be limited to centers where clinicians have received adequate training in the technique.

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

[O1] General approach

■ **RECOMMENDATION 58**

Children with GD should be treated with MMI, RAI therapy, or thyroidectomy. RAI therapy should be avoided in very young children (<5 years). RAI therapy in children is acceptable if the activity is >150 μCi/g (5.55 MBq/g) of thyroid tissue, and for children between 5 and 10 years of age if the calculated RAI administered activity is <10 mCi (<473 MBq). Thyroidectomy should be chosen when definitive therapy is required, the child is too young for RAI, and surgery can be performed by a high-volume thyroid surgeon. **Strong recommendation, moderate-quality evidence.**

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 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. Patient and parent values and preferences should also be strongly considered when choosing one of the three treatment modalities.

Because some children will go into remission, MMI therapy for 1 year is still considered first-line treatment for most children. However, the majority of pediatric patients with GD will eventually require either RAI 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 (see [P6] below) MMI, RAI, or surgery may be considered initially. If remission is not achieved after a course of therapy with ATDs, RAI or surgery should be considered. Alternatively, MMI

1856 therapy may be continued long-term, or until the child is considered old enough for
1857 surgery or RAI.

1858 Properly administered, RAI is an effective treatment for GD in the pediatric
1859 population (308-310). RAI is widely used in children, but still viewed as controversial by
1860 some practitioners owing primarily to concern over cancer risks (311,312). Although
1861 there are sparse clinical data relating to RAI use in children with GD and subsequent
1862 thyroid cancer (313), it is known that risks of thyroid cancer after external irradiation are
1863 highest in children <5 years of age, and they decline with advancing age (314,315); see
1864 discussion of RAI therapy and cancer risk in [P3] below. In comparison, activities of RAI
1865 used with contemporary therapy are not known to be associated with an increased risk of
1866 thyroid neoplasm in children.

1867 Thyroidectomy is an effective treatment for GD, but is associated with a higher
1868 complication rate in children than adults (316-318). Thyroidectomy should be performed
1869 in those children who are too young for RAI, provided that surgery can be performed by
1870 a high-volume thyroid surgeon, preferably with experience in conducting thyroidectomies
1871 in children.

1872 *Technical remarks:* There may be circumstances in which RAI therapy is
1873 indicated in young children, such as when a child has developed a reaction to ATDs,
1874 proper surgical expertise is not available, or the patient is not a suitable surgical
1875 candidate.

1876

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

[P1] Initiation of ATD therapy for the treatment of GD in children

■ **RECOMMENDATION 59**

MMI should be used in children who are treated with ATD therapy. **Strong recommendation, moderate-quality evidence.**

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%) (319). The MMI dose typically used is 0.2–0.5 mg/kg daily, with a range from 0.1–1.0 mg/kg daily (320-322). 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.

Although there may be a tendency to use higher rather than lower doses of MMI at treatment onset, data in adults show only modest benefit of higher doses, and only in severe thyrotoxicosis (free T_4 > 7 ng/dl (0.554 pmol/L)) (115). Because most side effects of MMI are dose-related, and occur within the first 3 months of treatment (128), high doses of MMI (e.g., >30 mg for an adolescent or adult) should rarely be used initially.

When thyroid hormone levels normalize, MMI doses can be reduced by 50% or more to maintain a euthyroid state (112). 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 (119,323), likely due to higher doses of MMI and the dose-related complications associated with MMI (324), we suggest that this practice be avoided. **However, it may have utility in rare patients, after addressing compliance, who are inadequately controlled on one dose of MMI, then become hypothyroid after a minimal dose increase.**

Practitioners should also monitor the weight of children treated with ATDs. Excessive weight gain within 6 months of treatment is seen in children treated for GD, and the gain in weight can persist (325). Parents and patients should be counseled about this possibility and nutrition consultation considered if excessive weight gain occurs.

■ **RECOMMENDATION 60**

Pediatric patients and their caretakers should be informed of side effects of ATD preferably in writing, 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. **Strong recommendation, low-quality evidence.**

■ **RECOMMENDATION 61**

Prior to initiating ATD 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. **Weak recommendation, low-quality evidence.**

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 (326,327). PTU can cause fulminant hepatic necrosis that may be fatal; liver transplantation has been necessary in some patients taking PTU (326). It is for this reason that the FDA issued a black box warning regarding the use of PTU (328), noting that 32 (22 adult and 10 pediatric) cases of serious liver injury have been associated with PTU use (326,328). Furthermore, since the recommendation was issued that PTU use in children be avoided, we are unaware of any published cases of PTU-related liver failure (327).

Because PTU-induced liver injury is of rapid onset and can be rapidly progressive, biochemical monitoring of liver function tests and transaminase levels has not been shown to be useful in surveillance for PTU-related liver injury. When neither prompt surgery nor RAI 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.

Prior to surgery it is desirable to have the free T_4, or total T_4 and total T_3 levels in the normal or subnormal range. Alternatively, if the surgery cannot be performed within a few weeks, a short course of PTU may be administered with the child closely monitored **clinically for signs of hepatic dysfunction including nausea, anorexia, malaise and abdominal pain.**

MMI may also be associated with hepatotoxicity in children, but this tends to be milder and is typically cholestatic rather than hepatocellular (326). There is at least one reported case of cholestatic jaundice in a child (326). However, there have been reports of hepatocellular toxicity with MMI in adults (134).

MMI may also be associated with antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (329), although this occurs far less frequently than with PTU. Patients of Asian origin seem to be more susceptible to this adverse reaction, and it can develop after months to years of therapy. Many PTU-treated patients also develop ANCA positivity on treatment, but remain asymptomatic (330). Typical manifestations of ANCA positive vasculitis are: polyarthritis, purpuric skin lesions, and occasionally pulmonary and/or renal involvement. Discontinuation of the drug generally results in resolution of the symptoms, but in more severe cases, glucocorticoids or other immunosuppressive therapy may be needed.

Technical remarks: It is advisable to provide information concerning side effects of ATDs to the patient **or caretaker** in writing. See Recommendation 14 *Technical remarks* for a discussion regarding the utility of obtaining complete blood count and liver profile before initiating MMI therapy.

[P2] Symptomatic management of Graves' hyperthyroidism in children

■ **RECOMMENDATION 62**

Beta adrenergic blockade is recommended for children experiencing symptoms of hyperthyroidism, especially those with heart rates in excess of 100 beats per minute. **Strong recommendation, low-quality evidence.**

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, metoprolol, or other beta-blockers leads to a decrease in heart rate and symptoms of GD. In those with reactive airway disease, cardio selective beta-blockers such as atenolol or metoprolol can be used cautiously (331), with the patient monitored for exacerbation of asthma.

[P3] Monitoring of children taking MMI

After initiation of MMI therapy, thyroid function tests (free T_4, total T_3, TSH) are obtained at 2-6 weeks, the dose is adjusted if indictated, and thyroid function tests are measured again at 4-6 weeks, and then every 2–3 months once the dose is stablized. Depending on the severity of hyperthyroidism and the MMI dose, it can take several months for elevated thyroid hormone levels to fall into the normal range. 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 63**

ATDs should be stopped immediately, and white blood counts measured in children who develop fever, arthralgias, mouth sores, pharyngitis, or malaise. **Strong recommendation, low-quality evidence.**

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 (332). MMI-related adverse events include allergic reactions, rashes, myalgias, and arthralgias (333,334), as well as hypothyroidism from overtreatment. Side effects from MMI usually occur within the first 3 months of starting therapy, but adverse events can occur later. In children, the risks of MMI-related cholestasis and hepatocellular injury appear to be much less than that observed in adults (326).

Agranulocytosis has been reported in about 0.3% of adult patients taking MMI or PTU (128,324,335). 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 (e.g., 5-10 mg/day) (128,324,335). When agranulocytosis develops, 95% of the time it occurs in the first 100 days of therapy (128,324,335). The overall rate of side effects **from** ATDs (both major and minor) in children has been reported to be 6%–35% (332,334,336,337).

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 for monitoring.

[P4] Monitoring of children taking PTU

■ **RECOMMENDATION 64**

In general, PTU should not be used in children. But, if used the medication should be stopped immediately and liver function and hepatocellular integrity assessed in children who experience anorexia, pruritus, rash, jaundice, light-colored stool or dark urine, joint pain, right upper quadrant pain or abdominal bloating, nausea, or malaise. **Strong recommendation, low-quality evidence.**

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. 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.

[P5] Management of allergic reactions in children taking MMI

■ **RECOMMENDATION 65**

Persistent minor cutaneous reactions to MMI therapy in children should be managed by concurrent antihistamine treatment or cessation of the medication and changing to therapy with RAI or surgery. In the case of a serious adverse reaction to an ATD,

prescribing the other ATD is not recommended. **Strong recommendation, low-quality evidence.**

If children develop serious adverse reactions to MMI, RAI or surgery should be considered because the risks of PTU are viewed to be greater than the risks of radioactive iodine or surgery. In special circumstances, where the patient is viewed to be at risk for thyroid storm and ATD therapy is needed in a child with a serious adverse reaction to MMI, PTU may be considered for short-term therapy to control hyperthyroidism. In this setting, families should be informed of the risks of PTU.

[P6] Duration of MMI therapy in children with GD

■ **RECOMMENDATION 66**

If MMI is chosen as the first-line treatment for GD in children, it may be tapered in those children requiring low doses after 1-2 years to determine if a spontaneous remission has occurred, or it may be continued until the child **and caretakers are** ready to consider definitive therapy, if needed. **Strong recommendation, moderate-quality evidence.**

The issue of how long ATDs should be used in children before considering either RAI 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 a lower chance of remission occurring with prolonged therapy (338). 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 (333,339,340).

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) or not Caucasian, serum TRAb levels are above normal on therapy, or free T_4 are substantially elevated at diagnosis (>4 ng/dL; 50 pmol/L) (339). One prospective study suggested that likelihood of remission could best be predicted by the initial response to ATDs, 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 studies (334,337).

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 (341), other studies of larger cohorts of pediatric patients with GD treated with ATDs for extended periods have not revealed similar remission rates (333,339,342). 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 (333). 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% (339,342).

More recently, in a retrospective analysis from Japan of 1,138 children, 723 were continued on long term ATD treatment, 271 underwent surgery or RAI, and 144 dropped out. Of the 639 patients of the 723 who discontinued ATD treatment, 46.2% achieved

2065 remission, and 34.2% relapsed. The prevalence of adverse events associated with MMI
2066 and PTU were 21.4% and 18.8%, respectively (343).

2067 In comparison, other recent studies of long term remission rates of pediatric GD
2068 treated with ATDs are very low (<20%), especially with longer follow-up, in cohorts
2069 from Germany (344) and Denmark (345).

2070 Data also suggest that there are age-related differences in responsiveness to
2071 ATDs. In one study that compared outcomes of 32 prepubertal and 68 pubertal children,
2072 remission occurred in only 17% of prepubertal children treated 5.9±2.8 years, compared
2073 with 30% of pubertal individuals treated 2.8±1.1 years (340). In another report, the
2074 course of GD was compared in 7 prepubertal, 21 pubertal, and 12 postpubertal children
2075 (336). Remission was achieved in 10 patients (28%) with similar rates among the three
2076 groups, whereas the time to remission tended to be longer in the small proportion of
2077 prepubertal children (median age, 6 years) (336).

2078 Persistence of GD in children is correlated with the persistence of TRAbs. A
2079 recent study found that TRAb levels normalized after 24 months in only 18% of pediatric
2080 patients on ATDs (346). There were no data showing that there was normalization of
2081 TRAb levels when patients were on ATDs for a longer time. Therefore, it appears that
2082 TRAb levels persist longer in children than in adults (346). Whereas monitoring of TRAb
2083 levels while on ATDs has been shown to be useful in adult patients for predicting the
2084 likelihood of remission or relapse of GD after stopping the medication (172), this
2085 approach has yet to be validated in children.

Whereas most studies, including recent large database reports (343), show that the vast majority of patients treated for GD with ATDs do not go into remission, a recent prospective report from France shows that with prolonged ATD use, remission rates of up to **49**% could be achieved. This study reported remision rates of 20%, 37%, 45%, and 49% after 4, 6, 8, and 10 years follow-up of 154 children treated with ATDs (337). The use of MMI in this group of children was associated with a very low rate of medication side-effects (337). Thus, whereas many practitioners will treat for 1-2 years with MMI, these data suggest that treatment for longer periods is also reasonable, as long as side-effects to medication do not occur.

■ **RECOMMENDATION 67**

Pediatric patients with GD who are not in remission following at least 1–2 years of MMI therapy should be considered for treatment with RAI or thyroidectomy. Alternatively, if children are tolerating ATD therapy, ATDs may be used for extended periods. This approach may be especially useful for the child not considered to be a candidate for either surgery or RAI. Individuals on prolonged ATDs therapy (>2 years) should be reevaluated **every 6-12 months** and when transitioning to adulthood. **Strong recommendation, low-quality evidence.**

If remission is not achieved upon stopping MMI after at least 1 or 2 years of therapy, RAI 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. As noted above, adverse reactions typically occur within the first few months of therapy.

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

[Q1] Preparation of pediatric patients with GD for RAI therapy

■ RECOMMENDATION 68

We suggest that children with GD having total T_4 levels of >20 ug/dL (260 nmol/L) or free T_4 >5 ng/dL (60 pmol/L) who are to receive RAI therapy be pretreated with MMI and beta-adrenergic blockade until total T_4 and/or free T_4 normalize before proceeding with RAI treatment. **Weak recommendation, low-quality evidence.**

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 RAI (347,348).

Technical remarks: When children receiving MMI are to be treated with RAI, the medication should be stopped 2-3 days before treatment (349). At that time patients should be placed on beta-blockers (if not already taking) until total T_4 and/or free T_4 levels normalize following RAI therapy, which generally takes 2-4 months. Although some physicians restart ATDs after treatment with RAI (80), this practice is seldom required in children (309,310,350). Thyroid hormone levels in children begin to fall within the first week following RAI therapy. ATDs can complicate assessment of post-

treatment hypothyroidism, since it could be the result of the MMI rather than the RAI therapy.

[Q2] Administration of RAI in the treatment of GD in children

■ **RECOMMENDATION 69**

If RAI therapy is chosen as treatment for GD in children, sufficient RAI should be administered in a single dose to render the patient hypothyroid. **Strong recommendation, moderate-quality evidence.**

The goal of RAI therapy for GD is to induce hypothyroidism, rather than euthyroidism, as lower administered activities of RAI result in residual, partially irradiated thyroid tissue that is at increased risk for thyroid neoplasm development (351). Because of an increased risk of thyroid nodules and cancer associated with low-level thyroid irradiation in children (314,352-354), and poor remission rates with low-administered activities of RAI (88-90), it is important that RAI activities >150 μCi (> 5.55 MBq/g) rather than smaller activities of RAI be administered to achieve hypothyroidism (312). With large glands (50–80 g), RAI activities of ^{131}I 200–300 μCi/g (7.4-11.1 MBq/g) may be needed (349). The administered activity of RAI to patients with very large goiters is high, and there is a tendency to underestimate the size of the gland (and thereby administer insufficient RAI activities to these patients) (90). Therefore, surgery may be preferable to RAI in children with goiters larger than 80 g.

Physicians at some centers administer a fixed dose of about 15 mCi RAI to all children (350), whereas others calculate the activity from estimation or direct

measurement of gland size and ^{123}I uptake (349). To assess thyroid size, particularly in the setting of a large gland, ultrasonography is recommended (355). There are no data comparing outcomes of fixed versus calculated activities in children; in adults, similar outcomes have been reported with the two approaches (356). One potential advantage of calculated versus fixed dosing is that it may be possible to use lower administered activities of RAI, especially when uptake is high and the thyroid is small. Calculated dosing also will help assure that an adequate administered activity is given.

When RAI activities >150 μCi/g (>5.55 MBq/g) are administered, hypothyroidism rates are about 95% (88,339,349). While there are reports that hyperthyroidism can relapse in pediatric patients rendered hypothyroid with RAI, this is very infrequent.

Technical remarks: RAI is excreted by saliva, urine, **perspiration, tears**, 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 RAI therapy. After RAI therapy, T_3, T_4, and/or 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 (333,349,350), at which time levothyroxine should be prescribed.

[Q3] Side-effects of RAI therapy in children

Side effects of RAI therapy in children are uncommon apart from the lifelong hypothyroidism that is the goal of therapy. Fewer 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 antiinflammatory agents for 24–48 hours (310,349).

If there is residual thyroid tissue in young children after RAI treatment, there is a theoretical risk of development of thyroid cancer. Detractors of the use of RAI 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 RAI therapy. The risk of thyroid neoplasia is greatest with exposure to low-level external radiation (0.1–25 Gy; ~ 0.09–30 μCi/g or 3.33-1110 Bq/g) (314,315,352,354,357), 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 RAI may have contributed to the increased risk of thyroid cancer in young children after the Chernobyl reactor explosion (315). Notably, thyroid cancer rates were not increased among 3,000 children exposed to RAI from the Hanford nuclear reactor site in an iodine-replete region (358). Increased thyroid cancer rates also were not seen in 6,000 children who received RAI for the purpose of diagnostic scanning (359).

There is no evidence to suggest that children or adults treated for GD with more than 150 μCi/g (5.55 MBq/g) of RAI have an increased risk of thyroid cancer directly attributable to RAI. While there are several studies of this issue in adults treated with RAI

for GD (see section [D2]), few studies have focused on populations exposed to RAI for the treatment of GD in childhood or adolescence.

In one study, an analysis was carried out of 602 individuals exposed to RAI below 20 years of age in Swedish and U.S. populations (360). The average follow-up period was 10 years, and the mean administered activity of RAI to the thyroid was 88 Gy (approximately 80 μCi/g or 2.96 MBq/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 RAI between 1953 and 1973 (100). 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 RAI varies with age, and the same absolute activities of RAI will result in more radiation exposure to a young child than to an adolescent or adult (361). At present, we do not have dosimetry information regarding RAI 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 RAI administered (361). Based on the Biological Effects of

Ionizing Radiation Committee VII analysis of acute, low-level radiation exposure (362) , the theoretical lifetime attributable risk of all-cancer incidence and all-cancer mortality for a large population of treated children can be estimated (Table 9).

To date, long-term studies of children treated with RAI for GD have not revealed an increased risk of nonthyroid malignancies. 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 RAI. Thus, we recommended above that RAI therapy be avoided in very young children (<5 years) and that RAI be considered in those children between 5 and 10 years of age when the required activity for treatment is <10 mCi (<370 MBq). 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 RAI 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 RAI administered should be based on thyroid size and uptake, and not arbitrarily reduced because of age in young individuals. Attempts to minimize the RAI activity will result in undertreatment and the possible need for additional RAI therapy and radiation exposure.

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

[R1] Preparation of children with GD for thyroidectomy

■ RECOMMENDATION 70

Children with GD undergoing thyroidectomy should be rendered euthyroid with the use of MMI. A potassium iodide **containing preparation** should be given in the immediate preoperative period. **Strong recommendation, low-quality evidence.**

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 RAI may be poor (88,90) and surgery also may be preferable for these patients. When performed, near-total or total thyroidectomy is the recommended procedure (363).

Technical remarks: MMI is typically given for 1–2 months in preparation for thyroidectomy. Potassium iodide (50 mg iodide/drop) can be given as 1-2 drops (i.e., 0.05–0.1 mL) three times daily for 10 days before surgery. SSKI can be mixed in juice or milk.

■ RECOMMENDATION 71

If surgery is chosen as therapy for GD in children, total or near-total thyroidectomy should be performed. **Strong recommendation, moderate-quality evidence.**

■ **RECOMMENDATION 72**

Thyroidectomy in children should be performed by high-volume thyroid surgeons.

Strong recommendation, moderately-quality evidence.

Surgical complication rates are higher in children than in adults, with higher rates in younger than in older children (316,318). Postoperatively, younger children also appear to be at higher risk for transient hypoparathyroidism than adolescents or adults (316,318).

Post-operative hypocalcemia requiring intravenous calcium infusions appears to occur more frequently than in in adults. Data from one center suggests that if calcitriol is started three days before surgery (0.25 or 0.5 mcg, bid), the need for post-operative calcium infusions is markedly reduced, leading to reduction in the length of stay (318). The calcitriol is then weaned over the first two post-operative weeks (318).

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 (316). 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 (318,364). 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.

[S] How should subclinical hyperthyroidism (SH) be managed?

[S1] Prevalence and causes of SH

The prevalence of SH in **an adult** population depends on age, gender, and iodine intake. In a representative sample of U.S. subjects without known thyroid disease, 0.7% had suppressed TSH levels (< 0.1 mU/L), and 1.8% had low TSH levels (< 0.4 mU/L) (365). Similar rates have been reported in studies from Europe, with higher levels in women and older subjects (366,367). The differential diagnosis of an isolated low or suppressed TSH level includes exogenous thyroid hormone use, nonthyroidal illness, drug effects, and pituitary/hypothalamic disease, all of which need to be ruled out before the diagnosis of SH can be established in a patient with an isolated low or suppressed TSH level. In addition, mean serum TSH levels are lower in black non-Hispanic Americans, some of whom may have slightly low TSH levels without thyroid disease (365). Finally, some otherwise healthy older persons may have low serum TSH levels, low normal serum levels of free T_4 and total T_3, and no evidence of thyroid or pituitary disease, suggesting an altered set point of the pituitary-thyroid axis (368,369).

The natural history of SH is variable (367,370-377), with annualized rates of 0.5 – 7% progression to overt hyperthyroidism and 5 – 12% reversion to normal TSH levels. In one study (372), 51.2% of patients had spontaneously developed a normal TSH when

first checked at some time within 5 years (mean time to repeat TSH 13 months). Progression from SH to overt hyperthyroidism appears more likely if the TSH is suppressed (< 0.01 mU/L), rather than low but detectable (0.01 – 0.4 mU/L) (375-377). Patients with GD rather than a TMNG as the cause of SH may be more likely to spontaneously remit (367,378). In patients at high risk of complications from SH, TSH and free T_4 should be repeated within 2-6 weeks. For all other patients, it is important to document that SH is a persistent problem by repeating the serum TSH at 3-6 months, prior to initiating therapy. In clinical series, TMNG is the most common cause of SH, especially in older persons (367,376,377). The second most common cause of SH is GD, which is more prevalent in younger persons, and is also common in patients who previously received ATD therapy. Other unusual causes include solitary autonomously functioning nodules, and various forms of thyroiditis, the latter of which would be more strictly termed ‘‘subclinical thyrotoxicosis.’’

[S2] Clinical significance of SH

Since SH is a mild form of hyperthyroidism, it is not surprising that deleterious effects seen in overt hyperthyroidism might also occur in SH. There have been a large number of recent studies elucidating these effects:

1. Overall mortality. A number of longitudinal studies have examined correlations between SH and overall mortality, with variable results. Some studies report increased overall mortality rates in SH subjects (374,379-383), especially older subjects, while others indicate no relation (384-387). Limitations of some of these studies include sample sizes, age ranges, length of follow-up, and diagnosis

of SH by a single TSH measurement. A recent meta-analysis of individual-level data from 52,674 participants, pooled from 10 cohorts and providing greater power, concluded that SH confers a 24% increased risk of overall mortality (388).

2. Cardiovascular disease. A recent large study of 26,707 people followed for 12 years reported increased cardiovascular mortality with SH (389). Some other, smaller studies have reached similar conclusions (374,383), although other smaller studies have failed to find a correlation (380,381,384,386). There have been two recent meta-analyses that examined this question, one of study-level data of 17 cohorts (390) and the other of individual-level data in 52,674 participants (388). Both analyses concluded that SH confers an increased risk of cardiovascular mortality, with hazard ratios of 1.52 (390) and 1.29 (388). In the individual-level meta-analysis, relative risks did not differ based on age, gender, pre-existing cardiovascular disease, or the presence of cardiovascular risk factors. However, the risk was greater in subjects with TSH levels < 0.1 compared to those with TSH levels 0.1 – 0.4 mU/L.

Some of these studies, including the meta-analyses, have also examined non-fatal cardiovascular events in SH, with similar increased risks (383,388,390,391). The most recent data indicate that SH subjects appear to be at particular risk for the development of heart failure (381,388,392), especially older subjects (381,392) and those with lower TSH levels (392). Mechanistic correlates of these findings include increased left ventricular (LV) mass and impaired LV function in SH that improve with treatment (393-396). In addition, two studies

have shown impaired glucose tolerance and decreased insulin sensitivity in SH, suggesting this may contribute to increased cardiovascular risk (397,398).

Arrhythmias are another concern in SH. Sawin et al first reported a 2.8-fold increased risk of atrial fibrillation in SH subjects over age 60 years in 1994 (399), and subsequent studies have confirmed that the risk of arrhythmias, particularly atrial fibrillation, is increased in SH (381,384,388,391,400,401). In the largest study to date (586,460 people followed for a median of 5.5 years), the highest relative risk for atrial fibrillation occurred in younger subjects, possibly because other causes predominate with age, and in subjects with lower TSH levels (401). However, absolute incidence rates of atrial fibrillation were much lower in younger subjects: for example, women under the age of 65 years had atrial fibrillation incidence rates of 2.3 events per 1,000 person-years (relative risk of 1.89 compared to age-matched euthyroid women), while women 65 years and older had incidence rates of 22.7 per 1,000 person-years (relative risk of 1.27 compared to age-matched euthyroid women). Similar trends were seen for men. A further population-based study found that SH increased the risk for stroke in subjects over age 50 years with a hazard ratio of 3.39 (402), although a recent meta-analysis of stroke risk in SH found insufficient number of events to draw definitive conclusions (403). Complementing these epidemiologic studies, investigations of smaller numbers of subjects with SH have revealed increased heart rate at rest and during exercise, decreased heart rate variability, and increased frequency of atrial and ventricular premature beats, which improve with treatment of SH (393,394,404,405).

Taken together, these data provide a strong argument for the treatment of SH in older subjects to avoid dysrhythmias and possible subsequent stroke. Whether younger patients should be treated for the same preventive indications is less clear. The most recent data provide evidence that relative risks of cardiovascular mortality and atrial fibrillation are elevated in younger, as well as older, patients with SH. However, the absolute risks of these events are very low in younger patients, so the risk/benefit ratio of treating younger SH patients is not clear. Clinical judgement should be used in these cases, and treatment decisions individualized.

3. Osteoporosis and fractures. Most studies of endogenous SH show decreased bone mineral density in post-menopausal women, but not in men or pre-menopausal women (406). However, it is not clear that this translates to increased fracture risk. A number of population-based studies have reported that certain groups of subjects with SH have increased fracture rates, including all adults (407), postmenopausal women (408), men (409), or subjects who progress to overt hyperthyroidism over time (391). The most recent and by far the largest individual study to date (231,355 people) reported a hazard rate for all major osteoporotic fractures combined (hip, humerus, forearm, spine) of 1.13 (confidence intervals 1.014-1.26). Risk increased with duration of SH, such that after a median follow-up of 7.5 years, 13.5% of subjects with a low TSH level had experienced at least one major osteoporotic fracture, compared to 6.9% of subjects with a normal TSH level (407). Other studies have not found increased fracture rates in SH subjects (410-412). A recent participant-level meta-analysis

of 13 cohorts (70,298 participants, median follow-up of 12.1 years) concluded that SH subjects had significantly elevated hazard ratios of 1.36 for hip fractures (6 vs. 4.9 fractures per 1,000 person-years) and 1.28 for any fractures (14.4 vs 11.2 fractures per 1,000 person-years) (413). Risks were further increased if TSH levels were < 0.1, compared to 0.1 – 0.44 mU/L, and if SH was due to endogenous etiologies, rather than thyroid hormone administration. Risks did not differ when stratified by age, although absolute fracture rates were lower in younger subjects. There are smaller, nonrandomized trials that have shown improvement in bone mineral density with therapy of SH with antithyroid drugs or radioactive iodine (414-417).

4. Mood and cognition. A large body of literature has investigated possible correlations between SH and cognitive decline (reviewed in (418), more recent studies (419,420)). Approximately equal numbers of studies report significant associations between SH and measures of cognitive decline and the development of dementia, vs. no associations. Therefore, at this time, no conclusions regarding this issue can be reached. There appears to be no correlation between SH and depression (421-423).

5. Physical functioning. Four studies have investigated whether SH is associated with self-reported functional capacity or objective measures of physical functioning (420,423-425). Three could find no correlation, while the fourth found a correlation between SH and lower physical performance in men only (425). Another uncontrolled study showed an increase in muscle mass and

muscle strength in middle-aged women with SH after treatment with RAI or thyroidectomy (426).

[S3] When to treat SH

■ **RECOMMENDATION 73**

When TSH is persistently <0.1 mU/L, treatment of SH is recommended in all individuals ≥ 65 years of age; in patients with cardiac risk factors, heart disease or osteoporosis; in postmenopausal women who are not on estrogens or bisphosphonates; and in individuals with hyperthyroid symptoms. **Strong recommendation, moderate-quality evidence.**

■ **RECOMMENDATION 74**

When TSH is persistently < 0.1 mU/L, treatment of SH should be considered in asymptomatic individuals < 65 years of age without the risk factors listed in recommendation 73. **Weak recommendation, moderate-quality evidence.**

Treatment of SH is controversial, since few intervention studies to show benefit have been performed, especially for clinically important endpoints such as cardiovascular events, atrial fibrillation, and fractures. Additionally, none of these studies included a control arm. Thus the evidence rests only with small uncontrolled studies that have shown improvements in cardiac structure and function, heart rate and the frequency of premature atrial and ventricular beats, bone mineral density, and muscle strength (393-396,405,414-417,426). In 2004, 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 (427). 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. Emerging epidemiologic data since then on risks for overall and cardiovascular-specific mortality, summarized above, have strengthened this argument, even in the absence of interventional data. The European Thyroid Association recently reviewed these data and published guidelines for the treatment of subclinical hyperthyroidism which are largely concordant with recommendations presented here (428).

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 (393). Although this study did not include younger individuals, the task force elected to recommend treatment of SH patients younger than 65 years of age with persistent TSH <0.1 mU/L and hyperthyroid symptoms. In the absence of symptoms or risk factors, treatment decisions must be individualized.

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 75**

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, osteoporosis, or symptoms of hyperthyroidism. **Weak recommendation, moderate-quality evidence.**

■ **RECOMMENDATION 76**

When TSH is persistently below the lower limit of normal but ≥ 0.1 mU/L, asymptomatic patients under age 65 without cardiac disease or osteoporosis can be observed without further investigation of the etiology of the subnormal TSH or treatment. **Weak recommendation, low-quality evidence.**

A number of the epidemiologic studies listed above performed analyses for SH subjects with low but detectable TSH levels (generally 0.1 to 0.4 mU/L). Some of these studies reported increased risks of overall mortality in older subjects (380,429), cardiovascular events (391), heart failure (381), and atrial fibrillation in all subjects (401) or in older subjects (384), and vertebral fractures in older women (408). However, there are no interventional data for or against treatment of individuals with serum TSH levels between 0.1 and the lower limit of the reference range. Therefore, treatment decisions must be individualized, based on the limited epidemiologic evidence and patient risk factors. The task force felt that the limited data are stronger for older subjects, and therefore treatment should be considered for older subjects, but is not recommended for subjects < 65 years of age. However, younger subjects should be monitored at regular 6-12 month intervals, and treatment should be considered if the TSH persistently decreases

to < 0.1 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 0.4 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 **before considering treatment** 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 10).

[S4] How to treat SH

■ **RECOMMENDATION 77**

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. **Strong recommendation, low-quality evidence.**

The treatment of SH is similar to the treatment of overt hyperthyroidism.

- RAI 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 RAI therapy. Given the low risk of exacerbation (71), the risks of ATD therapy may outweigh any potential small benefit.

- A course of ATD therapy is a reasonable alternative to RAI in patients with GD and SH, especially in younger patients, since remission rates are highest in persons with mild disease (109).
- Some patients with SH due to GD may remit spontaneously without therapy (375-377), 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 free T_4 and total 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 (430).

Technical remarks: Some patients with SH due to mild GD may remit spontaneously and may be followed without therapy with frequent (every 3-6 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.

[S5] 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. Based on the original indication for treatment, it is reasonable to follow hyperthyroid symptoms or

bone density (393,414-416); otherwise, the major end point is a TSH level within the age-adjusted reference range.

[T] How should hyperthyroidism in pregnancy be managed?

Normal pregnancy leads to changes in thyroid physiology that are reflected by altered thyroid function testing. In early pregnancy, these changes can mimic biochemical hyperthyroidism that does not require therapy (431). Hyperthyroidism due to GD occurs in 0.5-1.0 % of women in the reproductive age range (432), and 0.1-0.2 % of them are treated with ATD during pregnancy (433,434). Both the thyrotoxicosis and therapy of the disease may seriously complicate the course and outcome of pregnancy. In these guidelines, we will address only the most common issues related to hyperthyroidism in pregnancy, pending full guidelines on thyroid disease and pregnancy that are currently being updated by the ATA.

[T1] Diagnosis of hyperthyroidism in pregnancy

■ **RECOMMENDATION 78**

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 ranges increasing to 1.5 times above the nonpregnant range by the 2^{nd} and 3^{rd} trimester or free T_4 and total T_3 estimations with trimester-specific normal reference ranges. **Strong recommendation, low-quality evidence.**

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 serum free T_4 (or total T_4) and/or 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 different stages of pregnancy, and these changes may be assay-dependent.

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 non-pregnant reference range in the first half of a normal-term pregnancy (435,436), and especially so in gestational weeks 9-13, where a subset of pregnant women may develop suppressed serum TSH (437-439). The decrease in TSH in early pregnancy is the result of stimulation of the normal thyroid by high levels of serum human chorionic gonadotropin (hCG) (440), and occasionally the biochemical findings developing may correspond to **overt** thyrotoxicosis (gestational hyperthyroidism discussed below). However, low serum TSH levels with normal free T_4 (or total T_4) in early pregnancy do not indicate disease in need of therapy. During the second half of pregnancy, the lower limit of normal for TSH in the non-pregnant population can be used (441).

Free T_4 and T_3 measured in an equilibrium dialysate or an ultrafiltrate of serum around week 10 of pregnancy may be slightly higher (5–10%) than non-pregnancy values, corresponding to the period of high serum hCG and low serum TSH. From

normal or slightly elevated levels, a gradual decrease occurs during pregnancy, and late third trimester reference values are 10–30% below non-pregnancy values (442).

Serum total T_4 and T_3 increase in parallel in early pregnancy, primarily due to increases in TBG. In one longitudinal study, the increase in T_4 and T_3 reference ranges were observed to occur at a rate of 5% of non-pregnant values per week over the 10 week period of gestation weeks 7-16 (443). After this 50% increase, total T_4 and T_3 values remain stable with reference range limits 1.5 times above non-pregnancy ranges over the remaining weeks of pregnancy (442,443). 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. In the absence of these, consideration should be given to utilizing total T_4 and T_3 levels and multiply the non-pregnancy reference range by 1.5 **after week 16**, as discussed above.

Excluding patients with TSH suppression or gestational thyrotoxicosis during the first trimester, GD is the most common cause of hyperthyroidism during pregnancy (431,444); nodular thyroid disease is less common. Hyperthyroidism caused by a hCG-producing molar pregnancy or a choriocarcinoma presents with a diffuse hyperactive thyroid similar to GD, but without eye signs and without TRAb being detectable in serum. In these patients, serum hCG will be higher than expected, and the cause can be identified by obstetrical investigation.

Technical remarks: The reliability of automated analog-based assays for free T_4 and free T_3 has been questioned for more than 25 years (445), but these estimates are currently widely used because of their suitability for large scale automatic analyses within short time periods. 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, and in some assays give spuriously low results (446), method-specific reference ranges for each trimester of pregnancy should be used and provided by the manufacturer (447,448). If trimester specific references for free T_4 (and free T_3) are not provided, and total T_4 (and T_3) assays are not locally available, samples for thyroid function testing in pregnancy should be send to a reference laboratory.

[T2] Management of hyperthyroidism in pregnancy

Table 11 provides a summary of the recommendations concerning management of GD during pregnancy.

■ **RECOMMENDATION 79**

Transient hCG-mediated TSH suppression in early pregnancy should not be treated with antithyroid drug therapy. **Strong recommendation, low-quality evidence.**

Once the diagnosis of hyperthyroidism is made in a pregnant woman, attention should focus on determining the etiology and whether it warrants treatment. Clinical features that indicate the presence of 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 and self-limiting biochemical hyperthyroidism that may be observed in the first trimester of normal pregnancy. The disorder lacks the characteristics of Graves' disease (431), and is presumably caused by the high serum hCG of early pregnancy (440). It is not associated with adverse pregnancy outcomes (449). More severe degrees of gestational hyperthyroidism are associated with hyperemesis; affected women may develop biochemically overt hyperthyroidism and clinical symptoms and signs of hyperthyroidism. Complicated cases of gestational hyperthyroidism should be referred to medical centers with expertise in treating these patients.

Technical remarks: There is no evidence that treatment of gestational hyperthyroidism with ATDs is beneficial and use of ATD in early pregnancy has been associated with an increase in risk of birth defects. In these patients, physical examination and repeat thyroid function tests at intervals of 3–4 weeks is recommended. In the case of very symptomatic disease, a trial of beta blocker therapy (propranolol or metroprolol, but not atenolol (450,451)) for this transient disorder may be considered.

■ **RECOMMENDATION 80**

ATD therapy should be used for overt hyperthyroidism due to GD during pregnancy. PTU should be used when ATD therapy is given during the first trimester. MMI should be used when ATD therapy is started after the first trimester. **Strong recommendation, low-quality evidence.**

Untreated or insufficiently treated hyperthyroidism may seriously complicate pregnancy (452-454), 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 **in older assays** (47,455), **and 3% are negative in third generation assays** (57), especially those with milder disease.

A small increase in incidence of GD was found in early pregnancy in one study (456), and this fits the clinical observation that existing GD may occasionally worsen in early pregnancy (457). On the other hand, the incidence of GD drops dramatically in late pregnancy (456), which is consistent with the notion that thyroid autoimmunity improves in the second half of pregnancy (458).

Women who were treated with ATDs for GD and considered in remission after such previous therapy, and become pregnant, have a small risk of recurrence and should have their thyroid function tested in early pregnancy. In contrast, the risk of relapse (as well as the risk of thyrotoxicosis from postpartum destructive thyroiditis) during the postpartum period is relatively high (459), and it remains elevated for more than one year (456).

ATDs have much the same effect on thyroid function in pregnant as in non-pregnant women. Both ATDs and TRAb pass the placenta and can affect the fetal thyroid. On the other hand, T_4 and T_3 cross the placenta only in limited amounts, because of degradation by high deiodinase type 3 activities in the placenta (460).

PTU generally has been preferred in pregnancy because of concerns about well-documented teratogenicity associated with MMI, first described in 1972 (461). Defects that may be observed in 2-4 % of exposed children (462,463) have included aplasia cutis, choanal atresia, esophageal and other types of gut atresias, abdominal wall abnormalities including omphalocale, eye, heart, and urinary tract malformations. Moreover, typical facial features of MMI-exposed children have been described in case reports (464). In a US study, 31 % of women who had received MMI around the time of conception had elective termination of pregnancy versus 9 % of those who received PTU, and it was hypothesized that fear of MMI associated birth defects had led to the decision to terminate pregnancy (465).

Recently, an increase in the rate of birth defects (2.3 % above the background rate) was also observed after PTU exposure in early pregnancy (463), but these defects tended to be less severe than with MMI and included preauricular sinuses and cysts and urinary tract abnormalities (466). In a large group of children selected because they had major birth defects and had been exposed to some type of medication in early pregnancy, children exposed to PTU had a significantly higher frequency of situs inversus and cardiac outflow abnormalities than children exposed to other drugs (467), but these types of defects have not been observed in excess in studies comparing PTU exposed children with non-selected control children. Similar to other teratogenic drugs (468) the period of highest risk for birth defects from ATDs is gestational weeks 6-10 (469).

Concerns about rare but potentially fatal PTU-related hepatotoxicity have led The U.S. Food and Drug Administration to recommended that PTU be reserved for patients

who are in their first trimester of pregnancy, or who are allergic to or intolerant of MMI (157,470)

MMI and PTU both appear in breast milk in only small concentrations and studies of breast-fed infants of mothers taking ATDs have demonstrated normal thyroid function and subsequent normal intellectual development (109). 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.

As discussed in other sections of these guidelines, small doses of beta-adrenergic blocking agents are in general useful to reduce pulse rate and the hyperadrenergic symptoms of thyrotoxicosis during the time period from start of ATD therapy until the patient has become euthyroid. These agents have been studied extensively when used for treating hypertension in pregnancy, and no major side-effects have been detected, although fetal growth restriction has been associated with the prolonged use of especially atenolol (431,471). Therapy with propranolol (e.g. 10-20 mg every eight hour) or metopolol (e.g. 100 mg once daily) are useful and can be considered safe for short periods of time to relieve symptoms in pregnant women suffering from thyrotoxicosis.

■ **RECOMMENDATION 81**

In women who develop hyperthyroidism during their reproductive age range, the possibility and timing of future pregnancy should be discussed. Because of the risks of the hyperthyroid state on pregnancy and fetal outcome, we suggest that women should

postpone pregnancy until they have become euthyroid with therapy**. Strong recommendation, low-quality evidence.**

Both maternal thyroid dysfunction and therapy of the hyperthyroidism may have negative effects on the pregnancy outcome. These factors should all be considered when determining the choice of therapy for the patient who is currently pregnant, or in the future may become pregnant.

A single set of thyroid function tests within the reference range may not guarantee euthyroidism for more than a short period during the early phase of hyperthyroidism therapy. Two sets of tests within the reference range, taken with an interval of at least one month and without a change of therapy is preferable to indicate euthyroidism.

■ **RECOMMENDATION 82**

We suggest that women with hyperthyroidism caused by GD that require high doses of ATDs to achieve euthyroidism should be considered for definitive therapy before they become pregnant. **Weak recommendation, low-quality evidence.**

Both thyroidectomy and RAI therapy are useful for rendering patients with GD permanently hypothyroid with the possibility of a stable euthyroid state on thyroid hormone replacement therapy, as discussed in these guidelines. Thyroidectomy is often followed by **a decrease or** disappearance of TRAb from circulation, whereas RAI is often followed by a **transient** increase in TRAb. This is a potential argument in favor of surgical thyroidectomy in women with high TRAb titers that may become pregnant within the years to come, especially those planning therapy within the next year (172).

However, the importance of this difference in autoimmune activity for pregnancy outcome has not been studied, and it should be weighed against the other benefits and harms of surgery and RAI therapy.

To predict reduction in TRAb after surgical thyroidectomy, a recent retrospective Japanese study of 45 (41 female) patients with high TRAb (median 64 IU/L, range 5.6-400, normal for assay < 1.9 IU/L) may be useful. **Patients were followed** for 12 months. Smoking and the presence of orbitopathy predicted slow disappearance of TRAb (half-life 162 days, or 357 days if both factors were present), whereas TRAb levels in serum decreased with a half-life of 94 days in the remaining patients (472).

Medical tradition and experience with different types of therapy for GD varies between countries and clinics, and the risk of relapse of hyperthyroidism after ATD withdrawal may differ considerably, depending on iodine intake, and other factors that are only partly understood (473). Thus, advice given to women with GD on therapy in relation to a possible future pregnancy may differ. However, irrespective of such differences, the physician providing care to a young woman with newly diagnosed GD, should include discussion and guidance on GD and pregnancy. The severely hyperthyroid patient may not be in a position to fully comprehend many simultaneous messages, and a more detailed discussion may be appropriate when the patient has become euthyroid.

■ **RECOMMENDATION 83**

Women with hyperthyroidism caused by GD who are well controlled on MMI and desire pregnancy have several options:

a) Patients could consider definitive therapy before they become pregnant.

b) Patients could switch to PTU before trying to conceive.

c) Patients could switch to PTU as soon as pregnancy is diagnosed.

d) Appropriately selected patients could withdraw from ATD therapy as soon as pregnancy is diagnosed. If ATD therapy is withdrawn, thyroid function should be assessed weekly throughout the first trimester, **then monthly**. **Weak recommendation, low-quality evidence.**

The evidence is insufficient to give universal guidance on how to choose among these options, and therefore the potential risks and benefits of each option should be discussed with the patient, and patient values and preferences should be taken into account.

Each option is presented in depth in the following technical remarks:

A. Definitive therapy before becoming pregnant.

This strategy is discussed in Recommendation 82. It has the advantage of allowing the patient to become pregnant free of worry from the adverse fetal effects of ATDs. The disadvantage is that the patient will require levothyroxine therapy while pregnant and lifelong, and will be exposed to either the potential complications of RAI, including worsening or induction of Graves' orbitopathy, or the potential for undesirable surgical outcomes.

B. Switching from MMI to PTU before pregnancy.

Switching from MMI to PTU before conception would eliminate the risk from early pregnancy exposure to MMI in women where pregnancy is not recognized within the first few weeks after conception. MMI associated birth defects occur in 2-4 % of children exposed in early pregnancy, and abnormalities may be severe. PTU associated birth defects are less well documented. They may occur in 2-3 % of children but they seem to be mostly less severe. PTU is associated with liver failure with an estimated 1:10,000 risk of severe liver failure in adult patients (136). Thus, mothers must balance the risk of PTU to themselves vs. the risk to the child. Switching to PTU before conception may be preferred in younger women **with regular menses** who are expected to be able to conceive within 1 to 3 months. In a German prospective study of 340 such women, 68 % became pregnant within 3 months (474).

A special variant is women who have hyperthyroidism diagnosed at a time when they hope to become pregnant soon. There are not sufficient data to recommend for or against starting therapy with PTU and thus bypass a phase of MMI therapy in such patients.

C. Switching from MMI to PTU after conception.

Alternatively, the patient may continue MMI therapy but be prepared to detect pregnancy very early and modify therapy immediately as recommended below. Switching to PTU as soon as pregnancy is diagnosed may be preferred in older women

and women who have conditions that may be associated with delayed conception. This strategy may prevent prolonged use of PTU prior to conception but has the risk of fetal exposure to MMI if the diagnosis of pregnancy is delayed.

D. Withdrawing ATD treatment after conception.

Women with a stable euthyroid state on 5-10 mg MMI per day achieved within a few months, and a falling TRAb level are likely candidates to withdraw from ATD therapy in early pregnancy.

No study has directly addressed the risk of relapse of hyperthyroidism after ATD withdrawal in early pregnancy, and evidence comes from controlled or cohort studies of non-pregnant patients who had been treated with ATD for varying periods before drug withdrawal. Based on the latter studies, the risk of relapse of hyperthyroidism within a two month interval after ATD withdrawal in TRAb negative, non-smoking patients who have already been treated for 12-24 months is <10 % (167,475).

On the other hand, the risk of early relapse is very high in patients who have received ATD for less than six months, and/or still have indicators of high disease activity such as low serum TSH, high TRAb level, signs of active GO, or need of MMI dose in excess of 5-10 mg per day to remain euthyroid (473).

If ATD withdrawal is followed by a relapse of hyperthyroidism, this will often develop gradually over some weeks, but exact information on such time course in early pregnancy is not available. This is the reason for the recommendation of frequent thyroid

function testing during the remaining 1st trimester of pregnancy, until more data on safety becomes available.

A subset of women with GD will experience relapse of hyperthyroidism in pregnancy if ATD therapy is withdrawn according to recommendation 81. Frequent testing of thyroid function will allow early detection of such relapse and initiation of therapy with PTU **(or MMI if relapse occurs in the second trimester)** to keep the mother euthyroid. The risk to the mother from such hyperthyroidism is considered negligible.

Considering the fetus, two recent studies performed in Japan suggest that such transient and mild maternal hyperthyroidism will not increase the risk of malformations. One study observed a significantly lower risk of birth defects in mothers who had been shifted from MMI to iodine therapy in early pregnancy, even if part of the mothers in the iodine group had developed biochemical hyperthyroidism and needed retreatment with ATD (476). In another study from the same institution, the presence of a major birth defect was associated with the use of MMI in early pregnancy, but not with maternal thyroid dysfunction (462).

A more pertinent risk may be fetal loss caused by maternal hyperthyroidism in pregnancy (477,478). However, the risk from a brief period of mild maternal thyroid hyperfunction in early pregnancy may be low or absent. In a large cohort of pregnant women from the USA, low or suppressed serum TSH in early pregnancy (presumably mostly caused by early pregnancy high hCG levels) was not associated with adverse pregnancy outcomes (449). In the recent retrospective Japanese study of women with GD

2805 either treated with MMI in early pregnancy or shifted from MMI to iodine therapy in
2806 early pregnancy, there was no increase in fetal loss in the iodine group despite more cases
2807 of maternal hyperthyroidism in this group (476).

2808 ■ **RECOMMENDATION 84**

2809 We suggest that women who are treated with ATD and who may potentially become
2810 pregnant should be instructed to perform a pregnancy test within the first days after a
2811 missed or unusually light menstrual period. **Weak recommendation, low-quality**
2812 **evidence.**

2813 The period of major risk of birth defects caused by intake of medication in
2814 pregnancy is gestational weeks 6-10 (468), and a study of time of exposure to ATD and
2815 risk of defects suggests this is also the major period of teratogenic effects of ATD (469).
2816 Thus, withdrawal of ATD therapy **before** week five of pregnancy may theoretically
2817 prevent birth defects caused by ATD exposure.

2818 The week of pregnancy is calculated starting from the first day of the last normal
2819 menstrual period, with conception taking place about two weeks after this. The first real
2820 sign of pregnancy appears two weeks later, and it is a missed or unusually light menstrual
2821 period. By this time, blood and urine concentrations of hCG have started to rise and
2822 generally available pregnancy tests based on detection of hCG in urine normally become
2823 positive early in gestational week five. Very early testing for pregnancy to allow
2824 medication withdrawal before the major period of teratogenecity is recommended for
2825 other types of drugs that may be teratogenic (479).

■ **RECOMMENDATION 85**

We suggest that a woman who tests positive for pregnancy according to recommendation 84 contact the physician responsible for the ATD therapy **within 24 hours** to discuss future treatment options. **Weak recommendation, low-quality evidence.**

The time window that will allow medication withdrawal or change in early pregnancy to prevent birth defects is narrow (468,469), probably confined to gestational week 5. Thus, pregnancy should be detected early and action has to be taken immediately.

■ **RECOMMENDATION 86**

We suggest that the physician contacted according to recommendation 85 evaluate whether ATD withdrawal in the first trimester of pregnancy is likely to cause relapse of hyperthyroidism or not. Evaluation should be based on patient records, especially the severity of GD at time of diagnosis and current disease activity, duration of ATD therapy, current ATD dose requirement, and results of recent thyroid function and TRAb testing. If risk of relapse is considered low, therapy can be withdrawn, and followed by weekly thyroid function testing during the 1st trimester. **Weak recommendation, low-quality evidence.**

In the majority of patients with GD, ATD therapy is followed by a gradual remission of disease with a possibility of disappearance of TRAb from circulation (172). When patients have been treated with ATD for 12-18 months a rapid relapse of

hyperthyroidism after ATD withdrawal becomes less likely (119), even if the frequency of relapse may be in the order of 50 % within one year. The risk of relapse after ATD withdrawal varies considerably among individual patients and it depends on a variety of factors (473), as discussed in detail above.

■ **RECOMMENDATION 87**

We suggest that women in early pregnancy who have a high risk of recurrent or worsening hyperthyroidism if ATD is withdrawn be shifted from MMI to PTU immediately after diagnosing pregnancy. **Weak recommendation, low-quality evidence.**

Even if birth defects may occur after both MMI and PTU exposure in early pregnancy (463), defects after MMI exposure are better documented. The reason for this seems to be that MMI associated defects are more severe, whereas PTU associated defects tend to be less severe and may not be diagnosed immediately after birth (466).

Both MMI and PTU are effective therapies of hyperthyroidism in the majority of patients and the major effect of both drugs is to interact with thyroid peroxidase catalyzed thyroid hormone production (109). Apart from the differences in side-effects discussed above, it is important to consider differences in potency per mg drug and in duration of effect.

A dosage ratio of MMI to PTU of 1:20 is recommended when changing from one drug to another (115,319,480), although only two studies have examined this dosage ratio directly (115,319). Moreover, the difference in duration of effect should be taken into

account. For example, 15 mg of MMI would be roughly equivalent to 300 mg of PTU, but because the half-life of PTU is considerably shorter than that of MMI, the dose of PTU should be split over the day (481,482), e.g. MMI 15 mg once daily may be substituted with PTU 100 mg three times a day (319).

■ **RECOMMENDATION 88**

Women taking PTU during the 1st trimester of pregnancy according to recommendations 80, 83 or 87 may be switched to MMI at the beginning of the 2nd trimester, or they may continue PTU therapy for the remaining part of pregnancy if ATD is needed. **No Recommendation, insufficient evidence to assess benefits and risks.**

The reason for the FDA black box warning against PTU therapy after the 1st trimester of pregnancy is the risk of PTU associated liver failure. However, even if this risk is real, the absolute risk observed in studies of US health databases was low (433,465). Similarly, a recent Danish national registry study observed one case of reversible liver failure among 1,103 women treated with PTU in pregnancy (129).

The risk of side effects from PTU should be weighed against the risk of the shift from PTU to MMI inducing a transient thyroid function abnormality in the pregnant woman who is well controlled on PTU therapy. Starting from the 2nd trimester of pregnancy, women with GD may start entering gradual remission of the autoimmune abnormality, and full focus should be on the feasibility of ATD dose reduction to protect the fetus against goiter and hypothyroidism, as discussed below. Patients who remain on

PTU during the 2nd and 3rd trimesters could have hepatic enzymes measured at the same time that thyroid function is assessed. However, no prospective data show that this type of monitoring is effective in preventing fulminant PTU-related hepatotoxicity. Another aspect to consider is that both agranulocytosis and liver failure developing during MMI and PTU therapy mostly occur during the initial three months of therapy (128), but this risk can recur when the drug is reintroduced after a relatively long period of time (177). For example, in a Japanese study (177) of 14 patients who developed agranulocytosis after retreatment with the same ATD, no patient developed this adverse reaction who restarted the drug less than 5 months after stopping the previous course of therapy. There are no data to directly evaluate how shifting from PTU to MMI in the 2nd trimester of pregnancy will affect the risk of these severe, but rare side effects.

Other medical treatments for hyperthyroidism during pregnancy

Other types of medical therapy have been used to treat hyperthyroidism, such as iodine, perchlorate, cholestyramine, cholecystographic agents, and lithium.

Iodine in supraphysiological doses has multiple mostly inhibitory effects on the thyroid, and it has with some success been used to treat hyperthyroid women in pregnancy in Japan. In one study, cord and maternal sera were tested at delivery in 35 patients with GD treated with iodine (6-40 mg daily) initiated at 11-37 weeks of gestation. Similar to ATD therapy, thyroid function at term tended to be lower in the fetus than in the mother, but overall results of therapy were judged satisfactory, with a low risk of inducing hypothyroidism and goiter in the fetus; **only 1 of 35 neonates had subclinical hypothyroidism at birth** (483). In a recent study, outcomes of pregnancy

were retrospectively compared in 1,333 women who had continued ATD in early pregnancy with 283 women who had shifted from ATD to iodine (median gestational week of shift was week 6 (range 4-12)) (476). Overall, shifting had been more common in recent years. The prevalence of major birth defects was lower in the women who had shifted to iodine therapy (1.53 % versus 4.14 %, $p<0.05$). However, according to the authors, some degree of hyperthyroidism was relatively common after shifting, and free T_4 levels were always higher in the group that had shifted to iodine. Despite this, live births were more common in the group that had shifted than in the group that had continued MMI therapy (91.9 % versus 85.1 %, $p< 0.05$). In the publication, data on thyroid function in the MMI group are sparse, but the study may indicate that a brief period of mild hyperthyroidism in the mother will not impair pregnancy.

No recent data on iodine therapy for GD in pregnancy are available from outside Japan, but before ATDs became available, experience with iodine therapy for GD in general was extensive (484), and it corresponds to the more recent Japanese studies. The minimal effective dose of iodine was around 6 mg day but most patients received higher doses, iodine was effective for therapy of hyperthyroidism in patients with mild GD, but clearly less effective than ATD in patients with more severe disease (484). Additional data are needed before iodine therapy of pregnant women with GD can be generally recommended.

Perchlorate is a competitive inhibitor of iodine uptake by the thyroid, and a few cases have been published where it was used in pregnancy (485). Apparently, teratogenicity of perchlorate has not been demonstrated (486), but more clinical studies

on this are clearly needed. Further, this drug is not available in the United States.

Cholestyramine binds thyroid hormones in the gut during their entero-hepatic recirculation and has been used to treat hyperthyroidism, mostly in combination with other drugs (487,488). Cholestyramine is not absorbed from the gut and it is not expected to affect the fetus directly. However, binding in the gut and excretion of vitamins and other substances of importance for pregnancy is a concern, and has led to a note of caution by the US Food and Drug Administration. Cholecystographic drugs are not generally available any more. Lithium may be teratogenic (489) and it should not be used to treat hyperthyroidism in pregnancy.

■ **RECOMMENDATION 89**

GD during pregnancy should be treated with the lowest possible dose of ATD needed to keep the mother's thyroid hormone levels at or slightly above the reference range for total T_4 and T_3 values in pregnancy (1.5 times above non-pregnant reference ranges in the 2^{nd} and 3^{rd} trimester), and the TSH below the reference range for pregnancy. Similarly, free T_4 levels should be kept at or slightly above the upper limit of the pregnancy trimester reference range for the assay. Thyroid function should be assessed at least monthly, and the ATD dose adjusted, as required. **Strong recommendation, low-quality evidence.**

Even if the mother is euthyroid during ATD therapy, there is a risk of inducing fetal hypothyroidism and goiter during the second and third trimesters when the fetal

thyroid has begun to function (490,491). 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, and she is still in need of ATD therapy, the regimen should be changed to an ATD alone (444).

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 (444). In Japanese studies, ATD treated maternal free T_4 values had been kept above the non-pregnancy reference range in the last part of pregnancy to avoid cases of elevated TSH in newborn cord blood (458,491). However, with some automated free T_4 assays non-pregnancy free T_4 is much higher than late pregnancy free T_4 (446,492). Thus, maternal free T_4 above the non-pregnancy reference with suppressed TSH may leave the mother overtly hyperthyroid, which is not recommended.

Although many patients with GD may enter remission of the autoimmune abnormality during the 2^{nd} half of pregnancy with a need of ATD dose reduction or withdrawal, this is not a universal phenomenon. A small group of patients suffers from severe disease that may even progress during pregnancy, with difficult to treat hyperthyroidism, high TRAb levels and often a considerable goiter with high blood flow. Such patients may show a 'high T_3 - low T_4 pattern' during ATD therapy (444) presumably caused by a high type 1 deiodinase activity in the hyperactive thyroid (493), and preferential T_3 synthesis in the hyperstimulated thyroid made iodine deficient from

ATD therapy (494). Maternal thyroid function should be monitored frequently **and non-invasive assessment of fetal thyroid function (e.g. fetal heart rate, bone maturity, and fetal goiter on ultrasound),** and ATD therapy balanced to keep acceptable thyroid function in both the mother and the fetus (444).

■ **RECOMMENDATION 90**

Pregnancy is a relative contraindication to thyroidectomy and should only be used when medical management has been unsuccessful or ATDs cannot be used. **Strong recommendation, low-quality evidence.**

In a population based US study, pregnant women had worse clinical and economic outcomes following thyroid (and parathyroid) surgery than non-pregnant women, with disparities in outcomes based on race, insurance, and access to high-volume surgeons (68).

■ **RECOMMENDATION 91**

When thyroidectomy is necessary for the treatment of hyperthyroidism during pregnancy, the surgery should be performed if possible during the second trimester. **Strong recommendation, low-quality evidence.**

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) (67,68).

Evaluation by a high-risk obstetrician is advised along with counseling before surgery regarding risks involved (68). Thyroidectomy cures the hyperthyroidism and is often followed by a gradual reduction in circulating TRAb (495). 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 harbors TRAb after thyroidectomy, close fetal monitoring for both cardiovascular and skeletal changes with fetal ultrasound is essential.

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 relates to inhibition of iodine organification via the Wolff-Chaikoff effect. The fetal thyroid gland is particularly susceptible to the inhibitory effects of excess iodine **in the second half of gestation**, and fetal goiter can occur with chronic therapy (496). 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: In patients with difficult to treat hyperthyroidism, preoperative preparation for thyroidectomy during the second trimester of pregnancy includes 10 days of iodine (e.g., SSKI 1 drop three times a day), along with ATD therapy and beta-blockers (propranolol or metroprolol, but not atenolol (450,451)) to control hyperthyroidism (497-499). In euthyroid patients with no signs of high thyroid activity,

but who are offered surgical thyroidectomy for other reasons, e.g. intolerance to ATD, the use of iodine for surgical preparation is considered unnecessary.

[T3] The role of TRAb levels measurement in pregnancy

■ **RECOMMENDATION 92**

TRAb levels should be measured when the etiology of hyperthyroidism in pregnancy is uncertain. **Strong recommendation, low-quality evidence.**

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% (47).

■ **RECOMMENDATION 93**

Patients who were treated with RAI or thyroidectomy for GD prior to pregnancy should have TRAb levels measured using a sensitive assay initially during the first trimester thyroid function testing and, if elevated, again at 18-22 weeks of gestation. **Strong recommendation, low-quality evidence.**

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 (495,500). If the mother still produces TRAb, the antibodies 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 initially during the first trimester and, if elevated, again at 18–22 weeks of gestation. If the level is high, a program of fetal and neonatal surveillance for thyroid dysfunction should be initiated (501).

The advantage to initial TRAb measurement during the first trimester is that this allows time to initiate specialty consultation and, if the levels are especially high at that time, intervention may be required by the 2nd trimester. Whereas it has generally been considered that isolated fetal thyrotoxicosis in a previously ablated mother who is still producing TRAb might only start developing around weeks 20-22 of pregnancy, a recent case report described severe fetal thyrotoxicosis that had developed already in gestational week 18 (502). The pregnant women had previously undergone unsuccessful RAI, and subsequently a total thyroidectomy had been performed followed by L-T_4 replacement. The mother was now euthyroid, but her TRAb values remained extremely elevated.

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 RAI) and she is not currently taking ATDs (495,503).

■ **RECOMMENDATION 94**

Patients receiving ATD for GD when becoming pregnant or found to have GD during pregnancy should have TRAb levels measured at initial pregnancy visit or at diagnosis using a sensitive assay and, if elevated, again at 18-22 weeks of gestation. **Strong recommendation, low-quality evidence.**

TRAb (TBII or TSI) measurement may be useful to assist in the evaluation of disease activity in a woman being treated with ATDs for GD during pregnancy (444,495). 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, even if the mother is euthyroid on the medication.

■ RECOMMENDATION 95

Patients with elevated TRAb levels at 18-22 weeks of gestation should have TRAb remeasured in late pregnancy (weeks 30-34) to guide decisions regarding neonatal monitoring. An exception to this is a woman with an intact thyroid who is no longer in need of ATD therapy. **Strong recommendation, low-quality evidence.**

TRAb measurement in late pregnancy can be used to assess the risk of delayed neonatal hyperthyroidism, when the mother continues to need ATD to control hyperthyroidism up to term. After delivery, ATD 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. In a recent study of 47 newborns to mothers who were TRAb positive in pregnancy, nine of the children had neonatal biochemical hyperthyroidism, and five of these (9 % of all) needed ATD therapy. All hyperthyroid neonates were born to mothers with TRAb levels ≥ 5 IU/l (> 3 times upper reference for the assay) in the 2nd trimester (sensitivity 100%, specificity 43%). All mothers who gave birth to hyperthyroid newborns required ATD therapy in late pregnancy (504).

[T4] Postpartum thyroiditis

■ **RECOMMENDATION 96**

In women developing thyrotoxicosis after delivery, selective diagnostic studies should be performed to distinguish postpartum destructive thyroiditis from postpartum GD. **Strong recommendation, low-quality evidence.**

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 (505,506). 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 (506). 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 (507). In this study, tobacco smoking and bottle-feeding increased the risk of developing thyroiditis.

Postpartum thyroiditis must be distinguished from GD to recommend proper therapy. The postpartum surge in thyroid autoimmunity leading to postpartum thyroiditis is also associated with a 3-4 fold increase in the incidence of GD that peaks 3-12 months after delivery (456). In a Japanese hospital study, thyrotoxicosis caused by thyroiditis developed earlier post-partum than GD, although some overlap existed. All patients who developed overt thyrotoxicosis within the first three months after delivery suffered from destructive thyroiditis, whereas GD developed after this 3 months period (508). Goiter is generally more pronounced in GD, and thyroid bruit or GO strongly suggest GD as well. TRAb may occasionally be measurable in patients with postpartum thyroiditis, suggesting that some patients may suffer from a combination of GD and destructive thyroiditis (509), but higher TRAb values are suggestive of GD. When in vivo testing is required to make this distinction in women who are nursing, the gamma-emitters 123-I (half-life 13 hours) or Tc-99m- pertechnetate (half-life 6 hours) should be used rather than the beta-emitter 131-I (half-life 8 days). The shorter half-lives of these agents (510) will allow breast milk to be pumped and discarded for 10 half-lives (5 or 3 days respectively) and nursing resumed, whereas breast-feeding should ideally be discontinued 3 months prior to 131-I to avoid radiation exposure to the breast, and not be resumed if 131-I is given as treatment for GD (511).

Most often, the use of radioactive substances can be avoided and the diagnosis can be based on a combination of clinical presentation, TRAb measurement, and evaluation of serum T_4 and T_3. Thyroidal production of T_3 compared with T_4 is relatively high in GD, but not in destructive thyroiditis, and T_3 tends to be fractionally more elevated above the upper reference limit than T_4 in GD, whereas T_4 is more elevated than T_3 in destructive thyroiditis (50). If needed, thyroid color doppler ultrasonography may assist to distinguish between destructive thyroiditis and GD (508,512,513).

■ **RECOMMENDATION 97**

In women with symptomatic thyrotoxicosis from postpartum destructive thyroiditis, the judicious use of beta-adrenergic blocking agents is recommended. **Strong recommendation, low-quality evidence.**

Treatment for postpartum thyroiditis is generally supportive in nature, with the use of beta-adrenergic blockers such as propranolol or metroprolol to control pulse rate and hyperadrenergic symptoms during the thyrotoxic stage (514). The selective beta-1 adrenergic receptor-blocking agent atenolol should not be used in breast-feeding mothers because this may lead to symptoms consistent with beta-adrenergic blockage in neonates. This adverse effect presumably develops because atenolol is <5% bound to maternal plasma proteins (vs. 93 % binding of propranolol), and thus accumulates in milk, and because of low kidney excretion of atenolol in small children with immature renal function (515). Levothyroxine therapy may be beneficial, at least transiently, for women with symptomatic hypothyroidism or having TSH levels >10 mU/L (506).

Technical remarks: Because propranalol and metoprolol are secreted into breast milk in only very low levels, no special monitoring is needed for breastfed infants of mothers on these medications (514).

■ **RECOMMENDATION 98**

In pregnant women diagnosed with hyperthyroidism due to multinodular thyroid autonomy or a solitary toxic adenoma special care should be taken not to induce fetal hypothyroidism by ATD therapy. **Strong recommendation, low-quality evidence.**

Hyperthyroidism caused by thyroid autonomy is very common in people having current (or previous) mild to moderate iodine deficiency (13), but it mostly develops in patients after the age of 50 years. In the uncommon case of this type of hyperthyroidism in a pregnant woman, pathogenic differences from GD should be considered.

Thyroid hormone production in autonomy is dependent on iodine substrate, but no study has addressed the effect of a change in iodine intake on thyroid function in pregnant women with autonomy, or on the fetus. It might be beneficial to keep iodine intake on the low side, but care must be taken that the fetus is not iodine deficient, especially in areas where the population is iodine deficient. The degree of maternal hyperthyroidism and assessment of her diet should be considered before deciding whether to administer iodine supplements. Often the hormone overproduction is limited in patients with autonomy (50). In mild cases there would be a theoretical possibility that the normal pregnancy associated increase in thyroid hormone production may catch up with the hormone production in the

autonomous areas of the thyroid, and alleviate the need for ATD therapy. On the other hand, the high hCG levels in early pregnancy may theoretically stimulate the non-functioning normal thyroid tissue in these patients and worsen hyperthyroidism. Because there is no TRAb production, the fetal thyroid will not be abnormally stimulated in the second half of pregnancy as it is in GD. Thus, the fetus will not develop hyperthyroidism in parallel with the untreated hyperthyroid mother as it happens during 2nd half of pregnancy in GD, and neonatal hyperthyroidism is not a risk. On the other hand, the tendency to induce fetal hypothyroidism and goiter in the 2nd half of pregnancy from ATDs given to the mother would be even higher in this type of hyperthyroidism than in GD. Based on this theoretical risk, surgical therapy in the 2nd trimester of pregnancy may be considered if the hyperthyroidism turns out to require more than low dose MMI (5-10 mg per day) for control. No firm recommendations are given, because no good evidence is available.

[U] How should hyperthyroidism be managed in patients with Graves' orbitopathy?

GO is an inflammatory eye disease that develops in the orbit in association with autoimmune thyroid disorders (516). In the majority of cases (about 90%), it occurs in patients with current or past GD. Thyroid-associated orbitopathy, thyroid eye disease, and Graves' ophthalmopathy are other names used for GO. Approximately a third of patients with Graves' hyperthyroidism have some signs and/or symptoms of GO while only 5% suffer from moderate-to-severe disease (517,518). In contrast to GD where women are at higher risk, the role of gender in GO is more controversial. More recent studies do not

identify a clear gender related-risk for GO (517,518), while some older studies point to a possible slightly increased risk for men (519,520). This variability in results might be related to changes in smoking patterns over the years. The disease peaks in incidence in the 5th and 6th decade of life (517,518,521,522) with a higher prevalence of severe cases in the elderly population (517).

[U1] 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) (523,524), the elements of which are outlined in Table 12. The score ranges from 0 to 10 and predicts response to anti-inflammatory therapies (523,524). 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 $\geq$ 3. However, some of the eye changes seen in hyperthyroidism, like lid retraction or stare, are the result of the increased sympathetic state and when present without associated eye changes are not considered to reflect GO (69).

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 (525). Table 13 lists the elements as agreed upon in a consensus statement by the European Group on Graves' Orbitopathy (EUGOGO) (525). 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, keeping in mind that they do not always correlate,

particularly in early and late disease. The overall evaluation and management of GO is best done in a multidisciplinary clinic combining endocrinologists and ophthalmologists with expertise in the condition and other specialties in consultation (e.g., ENT, radiation therapy, plastic surgery, and endocrine surgery).

Quality of life is clearly impaired by GO (526). 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 two GO specific instruments published to date in North American populations (527,528), though the effect of GO therapy on these QoL scores still needs prospective data. Presently the only instrument that has such data is the instrument extensively used in Europe (529) that has not yet been tested in a North American population. Overall this area is in need of more research emphasis as despite its agreed upon importance a significant number of intervention trials in GO are still being reported without associated QOL outcomes (530).

In the remainder of section [U], 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 RAI as treatment for hyperthyroidism (Table 14).

[U2] Prevention of GO

Current therapeutic approaches to GO, including local measures, corticosteroids, orbital radiation, and surgery (525), 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 are listed in Table 15 and most pertinent to this discussion are RAI therapy for hyperthyroidism (531,532), untreated hyperthyroidism, smoking, high serum pretreatment TRAb levels (normal < 1.75 IU/L, high risk for progression if > 8.8 IU/Liter) (533), and **any delay in treating hypothyroidism after therapy for hyperthyroidism** (106,534). High pretreatment levels of T_3 and T_4 were each reported to have a predictive role in GO but these conclusions were not validated by subsequent studies (69,106,532,534) suggesting the possibility of higher TRAb values, measured on less sensitive assays early-on, being partly responsible for this variation.

■ **RECOMMENDATION 99**

Euthyroidism should be expeditiously achieved and maintained in hyperthyroid patients with GO or risk factors for the development of orbitopathy. **Strong recommendation, moderate-quality evidence.**

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 (535). Subsequently, two cohort studies in which patients received levothyroxine therapy early after RAI with the specific intent of preventing hypothyroidism noted that deterioration of GO rarely occurred (0%–2%) (534,536). A randomized study of newly diagnosed GD found that RAI, followed by active prevention of hypothyroidism by administration of thyroid

hormone 2 weeks later, did not increase the risk of worsening GO compared to therapy with MMI (RR of 0.95) (69).

■ **RECOMMENDATION 100**

We recommend clinicians advise patients with GD to stop smoking and refer them to a structured smoking cessation program. As both firsthand and secondhand smoking increase GO risk patients exposed to secondhand smoke should be identified and advised of its negative impact. **Strong recommendation, moderate- quality evidence.**

Smoking is the most important known risk factor for the development or worsening of GO, unrelated to type of therapy for GO (535), and consistent data from several studies show a detrimental effect of smoking on GO in patients treated with RAI (69,531). 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 (537).

Technical remarks: Clinicians should use smoking cessation programs based on effective and evidence-based approaches to aid in smoking cessation and avoidance of secondhand smoke (538,539).

[U3] Treatment of hyperthyroidism in patients with no apparent GO

■ **RECOMMENDATION 101**

In nonsmoking patients with GD without apparent GO, RAI therapy (without concurrent steroids), ATDs or thyroidectomy should be considered equally acceptable therapeutic options in regard to risk of GO. **Strong recommendation, moderate-quality evidence.**

Several randomized trials have identified the risk of GO development or progression after RAI therapy for hyperthyroidism to be between 10% and 39% (69,540). Focusing on the risk of new GO development that risk appears to be lower. Two randomized controlled trials found that risk to be 6/78 (8%) for RAI, compared with 1/74 (1%) for ATDs (531) in one study, and 10/32 (32%) for RAI compared with 6/56 (11%) for ATDs and 6/58 (10%) for surgery (532) in the older study. Fortunately, the cases of new or worse GO are usually mild with only 6/168 patients on this second trial (4 in the RAI group, 1 in the ATD group and 1 in the surgical group) requiring specific therapy for GO. In contrast, one prospective but nonrandomized cohort study identified no difference among ATD, surgery, and RAI treatment, with an overall 4.9–7.1% frequency of GO development (541). The higher risk of GO development after RAI therapy in the majority of studies may be related to the unique increase in TRAb levels observed following this therapy (172). Experimental evidence suggests that these antibodies are directly involved in GO pathogenesis (516,542,543).

There is evidence that corticosteroids given concurrently with RAI may prevent worsening of GO in patients with mild active eye disease (531). 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 (531). Table 14 details further the use of glucocorticoids for various GO clinical scenarios.

■ **RECOMMENDATION 102**

In smoking patients with GD without apparent GO, RAI therapy, ATDs, or thyroidectomy should be considered equally acceptable therapeutic options in regard to risk of GO. **Weak recommendation, low-quality evidence.**

■ **RECOMMENDATION 103**

There is insufficient evidence to recommend for or against the use of prophylactic corticosteroids in smokers who receive RAI and have no evidence of GO. **No recommendation, insufficient evidence.**

However, in two different studies, active smokers who received RAI represented the group with the highest incidence (23–40%) of new GO or deterioration of pre-existing GO during 1 year of follow-up (69,531).

[U4] Treatment of hyperthyroidism in patients with active GO of mild severity (see Tables 12 and 13 for definitions of disease activity and severity)

■ **RECOMMENDATION 104**

In patients with Graves' hyperthyroidism who have mild active ophthalmopathy and no risk factors for deterioration of their eye disease, RAI therapy, ATDs and thyroidectomy should be considered equally acceptable therapeutic options. **Strong recommendation, moderate-quality evidence.**

■ **RECOMMENDATION 105**

In the absence of any strong contraindication to GC use we suggest considering them for coverage of GD patients with mild active GO who are treated with RAI, even in the absence of risk factors for GO deterioration. **Weak recommendation, low-quality evidence.**

Technical remarks: The decision whether or not to administer concurrent glucocorticoids in a particular patient choosing RAI therapy should be made in light of risk–benefit considerations (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 ATDs or surgery. Besides smoking, the main risk factors for deterioration of GO to be considered in this decision include active and progressive GO over the preceding 3 months and high serum pretreatment TRAb levels (normal < 1.75 IU/L, high risk for GO progression if >8.8 IU/Liter) (see Table 15).

The dose of corticosteroids validated in a randomized clinical trial for GO prophylaxis is the equivalent of prednisone 0.4–0.5 mg/kg/day, started 1–3 days after RAI administration, continued for 1 month, and then tapered over 2 months (525). However, a retrospective cohort study suggested that even 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, (544). Currently most task force members use a minimum starting dose of 30 mg prednisone daily and tapering to off within 6-8 weeks. Table 14 details further the use of glucocorticoids for various GO clinical scenarios.

■ **RECOMMENDATION 106**

In GD patients with mild GO who are treated with RAI we recommend steroid coverage if there are concomitant risk factors for GO deterioration. **Strong recommendation, moderate-quality evidence.**

Unfortunately, the initial data regarding the impact of various GD therapies on GO outcome were impacted by the absence of GO activity assessment and lack of stratification on smoking status at randomization as well as by variation in the timing of tackling post-RAI hypothyroidism. Two early nonrandomized studies found no differences between the three GD therapeutic modalities (541,545).

The first randomized study of GD patients (13% with mild preexistent GO) assigned to therapy for hyperthyroidism with antithyroid drugs, surgery or RAI (532) found the relative risk for deterioration of eye disease to be elevated at 3.2 for RAI

compared to ATDs. There appeared to be no difference in such risk between ATDs and surgery. A more recent large randomized controlled trial studying mainly patients with previously treated GD showed RAI therapy to be associated with an increased risk of GO progression (RR of 5.8 in comparison with ATDs) and found the risk to be eliminated with concurrent corticosteroid administration (531). Finally, the most recent randomized controlled trial (69) revealed the increased risk for new or worse GO in RAI treated patients (38.7% of the group) compared with ATD-treated patients (21.3% of the group), to be mainly related to development of new GO cases while worsening of preexistent GO occurred in a similar percentage in both groups (45% for RAI and 47% for ATD). Smoking was a strong risk factor for an undesirable GO outcome. In this last trial there was no routine use of prophylactic glucocorticoids. Table 14 details further the use of glucocorticoids for various GO clinical scenarios.

[U5] Treatment of hyperthyroidism in patients with active and moderate-to-severe or sight-threatening GO (see Tables 12 and 13 for definitions of disease activity and severity)

■ **RECOMMENDATION 107**

In patients with active and moderate to severe or sight-threatening GO we recommend against RAI therapy. Surgery or ATDs are preferred treatment options for GD in these patients. **Strong recommendation, low-quality evidence.**

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 (546). 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 (547), suggesting that surgery is not detrimental to GO and may be associated with improvement in some patients. Additionally, a more recent study suggests that surgery might lead to a more rapid improvement in GO than ATDs and it might thus be a better option for patients that are most concerned about GO changes (548). Other studies suggest that ATDs may not adversely impact mild active GO, but do not address severe GO (531).

Alternatively, if ATDs are selected for GD therapy there is reassuring data that long term use is relatively safe and effective at preserving euthyroidism while waiting for GO to enter remission (66,549).

[U6] Treatment of GD in patients with inactive GO (see Table 12 for definition of disease inactivity)

■ **RECOMMENDATION 108**

In patients with inactive GO we suggest RAI therapy can be administered without steroid coverage. However, in cases of elevated risk for reactivation (high TRAb, CAS ≥1 and smokers) that approach might have to be reconsidered. **Weak recommendation, low-quality evidence.**

There is a low rate of GO progression or reactivation following RAI in patients with inactive GO. A series of 72 patients with inactive GO according to the CAS were treated with RAI without concurrent glucocorticoid administration (536). In those whom hypothyroidism was prevented by early thyroxine therapy, no deterioration in eye disease was reported (536). Smoking history did not impact GO outcome in this cohort. A recent trial from Japan (540) randomized patients without GO or inactive GO (i.e. CAS<3 or T2-weighted imaging T2SIR ≤1) to receive either glucocorticoid prophylaxis with low dose prednisolone (on average 0.28 mg/kg/day tapered rapidly over 6 weeks) or no prophylaxis at all. The rate of disease progression in the absence of risk factors was low (4.2%) and not impacted by glucocorticoid therapy. The presence of risk factors for GO (high thyroid stimulating antibody, CAS≥1) increased that risk, again without a benefit from low-dose steroid prophylaxis. Ultimately most GO cases were mild and only 7 cases (2.4%) required GO-directed therapy. Whether high-dose glucocorticoid therapy would have made a difference in these patients is not known.

Another study retrospectively examined the impact of concurrent oral or intravenous glucocorticoid therapy on the development or deterioration of preexistent GO after RAI therapy for relapsing GD patients (550). They identified GO development, deterioration or reactivation in approximately 7% of patients (6/83) considered at low risk who were given no steroid prophylaxis. Only 2 of these cases had preexistent inactive GO. Despite prophylaxis, 33% of patients considered at high risk who were treated with oral glucocorticoids had worsening of GO. However, because of the lack of clarity of this retrospective study regarding prevalence of active and inactive GO in each group and the lack of pre-specified criteria for dose and route of steroid use in those considered at risk,

we weighed this evidence less in our deliberations regarding the above recommendation. Table 14 details further the use of glucocorticoids for various GO clinical scenarios.

[V] How should iodine–induced and amiodarone-induced thyrotoxicosis be managed?

[V1] Iodine-induced hyperthyroidism

■ RECOMMENDATION 109

Routine administration of ATDs before iodinated contrast media exposure is not recommended **for all patients**. **Weak recommendation, low-quality evidence.**

Technical remarks: Patients deemed to be at high risk of developing iodine-induced hyperthyroidism or whose cardiac status is tenuous at baseline may be considered for prophylactic therapy with ATDs.

Iodine-induced hyperthyroidism (the Jod-Basedow phenomenon) is uncommon in modern series, and generally self-limited, but may occasionally persist for months (551,552), and may be life-threatening (553-556). Individuals most susceptible are elderly patients with autonomously-functioning nodular goiters (557), and less commonly, patients with occult GD (558), or patients with a prior history of GD and in remission after a course of ATDs (559). Very rarely, iodine excess may trigger thyrotoxicosis in patients with a previously normal thyroid gland (560). Chronic iodine deficiency increases the prevalence of autonomous thyroid nodules and therefore iodine

repletion in this setting has historically been linked to iodine-induced hyperthyroidism (561).

Multiple observational studies have examined changes in thyroid hormone levels following a single exposure to intravenous iodinated contrast in both iodine-sufficient (562-565), and deficient (566-569) regions. A study of patients living in Boston showed that 5 of 49 (10.2%) developed a suppressed TSH value 1-4 weeks following exposure to a single CT study with contrast, with only one patient developing overt hyperthyroidism (565). Additional observational studies in the United States and Japan, involving 56 and 22 patients, respectively, found no new cases of hyperthyroidism following coronary angiography (564) or hysterosalpingography (563), whereas an Australian study from a region of iodine sufficiency found that 2 of 72 (2.8%) of patients developed overt hyperthyroidism and an additional 2 developed subclinical hyperthyroidism within 8 weeks of iodinated contrast exposure (562). Overall, similar rates of iodine-induced hyperthyroidism have been described in iodine deficient regions, including a study from Germany in which 2 of 788 (0.25%) patients developed overt hyperthyroidism following coronary angiography (566), a New Zealand study in which subclinical hyperthyroidism developed in 2 of 102 (2%) patients after a CT-scan with iodinated contrast (567), a study from Italy which found that 1.9% of 1752 patients undergoing coronary angiography developed a suppressed TSH with normal free T_4 and T_3 levels (568), and finally, a Turkish study identifying new subclinical hyperthyroidism in 5.9% of 101 patients by 8 weeks following coronary angiography (569).

A recent case-control study in the United States found that iodinated contrast exposure in patients without baseline thyroid abnormality resulted in hyperthyroidism (defined only as a suppressed TSH value) with an odds ratio of 1.98 (95% CI, 1.08-3.60; P = .03), and that 23 patients would need to be exposed before encountering one case of iodine-induced thyrotoxicosis (570). Interestingly, a recent meta-analysis including 9 randomized-controlled trials and 8 observational studies involving iodine supplementation of young children and pregnant women in regions of mild-moderate iodine deficiency did not find an increased risk of thyroid dysfunction following iodine supplementation of 200-300 micrograms daily (571).

In summary, iodine-induced hyperthyroidism is uncommon and generally subclinical, but can occasionally be severe. For most clinical circumstances, the likelihood of developing overt thyrotoxicosis after iodinated contrast exposure is too low to justify the risk of adverse effects associated with prophylactic ATD therapy.

■ **RECOMMENDATION 110**

Beta-adrenergic blocking agents alone or in combination with MMI should be used to treat overt iodine-induced hyperthyroidism. **Strong recommendation, low-quality evidence.**

Treatment of iodine-induced hyperthyroidism includes avoidance of additional iodine and administration of beta-blockers alone or with ATDs, depending on the severity of hyperthyroidism and the clinical status of the patient. RAI is not an option until the iodine load has been cleared and might not be desirable given the reversibility of this

condition. Recent data suggest that urinary iodine normalizes more rapidly than previously believed, with a return to baseline urinary iodine excretion within 1-2 months in most patients (565,572).

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 ATD in patients with iodine-induced hyperthyroidism. Urinary iodine **(a spot urine iodine adjusted for urine creatinine concentration or a 24-hour urine iodine)** may be monitored to assess the rate of clearance of the iodine load.

[V2] Amiodarone-induced thyrotoxicosis

■ **RECOMMENDATION 111**

We suggest monitoring thyroid function tests before and within the first 3 months following the initiation of amiodarone therapy, and at 3–6 month intervals thereafter. **Weak recommendation, low quality evidence.**

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 (573-575) and in up to 10% in iodine-deficient areas, such as parts of Europe (576). Studies evaluating the adequacy of monitoring for adverse effects from amiodarone have shown suboptimal results (577,578).

Two distinct mechanisms have been proposed in the development of AIT, including an iodine-induced form of hyperthyroidism (type 1 AIT) due to the high iodine content of amiodarone (37% by molecular weight), and a destructive thyroiditis (type 2 AIT), due to direct toxicity of amiodarone on follicular cells. Type 1 AIT tends to occur in patients with underlying thyroid autonomy in a nodular goiter, or GD, whereas type 2 AIT occurs as a result of direct damage or induction of apoptosis in thyrocytes by amiodarone (579-582).

■ RECOMMENDATION 112

The decision to stop amiodarone in the setting of thyrotoxicosis should be determined on an individual basis in consultation with the treating cardiologist, based on the clinical manifestations and presence or absence of effective alternative antiarrhythmic therapy. **Strong recommendation, low-quality evidence.**

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, (iii) amiodarone may have T_3-antagonistic properties at the cardiac level and inhibit T_4 to T_3 conversion in the heart (583) , such that withdrawal may actually aggravate cardiac manifestations of thyrotoxicosis (573). Deaths from ventricular fibrillation have occurred after stopping amiodarone in patients with AIT (584). In addition, type 2 AIT typically responds to treatment even if amiodarone therapy is continued (585-587), but continuation may lead to a more prolonged time to recovery and a higher rate of future recurrences of AIT (588).

■ **RECOMMENDATION 113**

In clinically stable patients with AIT, we suggest testing to identify disorders associated with iodine-induced hyperthyroidism (type 1 AIT), specifically including toxic nodular disease and previously occult Graves' disease. **Strong recommendation, low-quality evidence.**

■ **RECOMMENDATION 114**

MMI should be used to treat overt thyrotoxicosis in patients with proven underlying autonomous thyroid nodules or Graves' disease as the cause of amiodarone-induced thyrotoxicosis (type 1 disease), and corticosteroids should be used to treat patients with overt amiodarone-induced thyroiditis (type 2 disease). **Strong recommendation, low-quality evidence.**

■ **RECOMMENDATION 115**

Combined ATD and corticosteroid therapy should be used to treat patients with overt amiodarone-induced thyrotoxicosis who are too unstable clinically to allow a trial of monotherapy, or who fail to respond to single modality therapy, or patients in whom the etiology of thyrotoxicosis cannot be unequivocally determined. **Strong recommendation, low-quality evidence.**

As the pathogenesis of AIT is not fully understood, it is likely that the classic division of AIT into two subtypes represents an oversimplification. First, as discussed

further below, many patients are not readily classified into one of the two AIT subtypes. Secondly, once classified as type 1 or type 2 AIT, patients often fail to respond to therapy specifically directed to that subtype (583,589,590). Finally, findings of responsiveness of type 2 AIT patients to measures not typically useful in destructive thyroiditis, such as perchlorate (586,591) and oral cholecystographic agents (592,593), cannot be adequately explained on the basis of the current classification system, although spontaneous resolution independent of therapy is one possible explanation.

A number of methods have been examined to distinguish type 1 from type 2 AIT, but with the possible exception of Color flow Doppler study (CFDS), most are considered unreliable (574). For example, the T_3-to-T_4 ratio, which tends to be higher in patients with autonomous thyroid glands than in those with destructive thyroiditis, is not helpful in this instance due to amiodarone-associated inhibition of T_4 monodeiodination (594). Further, features historically used to distinguish the subtypes such as antibodies against thyroid peroxidase and the presence of thyroid nodules in patients with type 1 AIT may actually occur with both subtypes, given the prevalence of these abnormalities in the general population. Interleukin-6 levels and radioactive iodine uptake values, once promoted as useful to distinguish between subtypes (590), actually overlap extensively between the two subtypes and are therefore also not useful (594). Several modern series of patients with AIT make no attempt to classify patients into type 1 or type 2 disease (585,595-598).

Several studies have shown that increased vascularity on color-flow Doppler study may be seen in patients with type 1, but not type 2 AIT (599-601). Two studies

showed a clear separation into type 1 and type 2 AIT, allowing successful application of targeted therapy (599,600). However, CFDS is not universally useful (584,589) In a series of 24 cases of AIT, 12 patients were classified as type 2 due to an absence of vascularity (CFDS 0) and treated with corticosteroids, but only 7 (58%) proved responsive (584). Likewise, these authors found that among 11 patients classified as type 1 AIT based on CFDS scores of I-III, only 4 (36%) responded to antithyroid drug therapy. In another series of 30 patients with AIT requiring therapy, 10 (33%) patients could not be subtyped on the basis of CFDS, including several patients with goiters but normal vascular flow (589). In a series of 55 patients in whom a CFDS qualitative assessment of vascular flow was used to distinguish type 1 from type 2 AIT, 81.3% of patients determined to have type 1 AIT had pattern I vascularity (the lowest level above zero), illustrating the skill and nuance needed to successfully make this distinction (599). Among European thyroidologists surveyed on the use of diagnostic imaging in the differential diagnosis of AIT, approximately 20% preferred RAIU alone, 20% preferred CFDS alone, nearly 40% utilized both methods simultaneously, and 20% thought both techniques were useless (602). Recently sestamibi uptake by the thyroid, which is diminished with thyroiditis, has been applied to distinguishing AIT subtypes with preliminarily promising results (603,604).

A recent retrospective report including 200 AIT patients found that the onset of thyrotoxicosis was significantly earlier in type 1 (median 3.5 months, range 1-61 months) than type 2 (median 30 months, range 1-95 months), $p< 0.001$ (605). Since 80% of type 1 patients in this study had autonomous thyroid nodules or toxic MNG, it is not unexpected that iodine-induced thyrotoxicosis occurred early in the course of amiodarone

therapy. However, based on this data, a patient with late-onset of AIT in whom GD has been excluded is more likely to have type 2 AIT. Another observation reported in this study is the development of AIT following amiodarone discontinuation. Nineteen percent of patients (38/200) developed AIT a mean of 5.5 months after the drug was stopped, 36 of whom had type 2 AIT.

Patients who are clinically stable and have definite evidence supporting a distinct subtype of overt AIT may be tried on appropriate monotherapy. When identified with certainty, type 1 AIT is best treated with MMI to prevent new hormone synthesis and, rarely, with added potassium perchlorate (250 mg four times daily; not available in the United States) (590). Type 2 AIT is better treated with anti-inflammatory therapy such as prednisone, with improvement occasionally seen as early as 1 week, and usually within a few weeks (590). As noted above, some patients with mild type 2 AIT (approximately 20%) resolve spontaneously without stopping amiodarone or administering corticosteroids (606,607).

Most series of patients with AIT contain cases in which sequential therapy for both subtypes was required before resolution of AIT occurred. These patients are frequently referred to as “mixed” types of AIT. In a study of 20 patients with AIT that included both type 1 and type 2 patients, perchlorate was administered alone for 1 month, resulting in euthyroidism in 12 patients (7 with type 1 AIT and 5 with type 2 AIT) (591). Corticosteroids were then given to the eight nonresponders (including 7 patients with presumed type 1 disease), and euthyroidism was achieved in all after an average of approximately 6 weeks (591). Patients are often reclassified retrospectively from type 1

to type 2 AIT based on a positive response to corticosteroid therapy or after an outcome of permanent hypothyroidism, both of which would be unlikely in iodine-induced thyrotoxicosis (598,606). Patients recovering from apparent type 2 AIT should be monitored for permanent hypothyroidism, which appears to occur more often with AIT than with subacute thyroiditis (608).

Importantly, individuals with moderate thyrotoxicosis and compromised cardiac status should be considered for initial combined therapy rather than sequential empiric therapy. Some centers recommend starting combined therapy with antithyroid drugs and corticosteroids at the time of initial AIT diagnosis (594,609), and between 16-25% of surveyed thyroidologists prefer combination antithyroid drug and corticosteroid therapy for patients with apparent type 2 AIT (610). A rapid response to combined corticosteroid and antithyroid drug therapy is believed to favor type 2 AIT (594) and allows a reduction in antithyroid drugs, although some patients with type 2 AIT have a prolonged course, particularly those with larger thyroids or worse thyrotoxicosis at the time of diagnosis (611). A suggested approach to the management of AIT is shown in **Figure 1**.

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 116**

Patients with AIT who are unresponsive to aggressive medical therapy with MMI and corticosteroids should undergo thyroidectomy. **Strong recommendation, low-quality evidence.**

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 (612). Thyroidectomy done under regional anesthesia when available may be preferred for very ill patients (613). Several surgical series involving patients with AIT have now been published, with generally favorable results (612,614-616). Patients in whom amiodarone was stopped during an episode of AIT should be considered for definitive therapy with RAI or surgery in order to facilitate reintroduction of amiodarone without concerns about recurrent AIT (617).

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

Several varieties of thyroiditis can present with temporary thyrotoxicosis as part of a classic triphasic course (thyrotoxicosis, hypothyroidism, recovery), including subacute thyroiditis, painless (silent) thyroiditis, acute (suppurative) thyroiditis, palpation (traumatic) thyroiditis, postpartum thyroiditis, and drug-induced thyroiditis. In general, thyroid dysfunction caused by thyroiditis is less severe than that seen with other forms of endogenous thyrotoxicosis (50); RAIU is universally low during the thyrotoxic stage,

owing to leaking of preformed thyroid hormone with suppression of serum TSH concentrations. In this section, subacute, painless, acute and palpation thyroiditis will be discussed; see section [T4] for a discussion of postpartum and section [X] for a discussion of drug-induced thyroiditis.

[W1] Subacute thyroiditis

Subacute thyroiditis, also called subacute granulomatous or de Quervain thyroiditis, is a common cause of thyroid pain (24). The diagnosis of subacute thyroiditis is based on clinical history, physical examination, laboratory data, 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 from one side to the other of the gland over several weeks. Patients may have a prodrome of malaise, low-grade fever, pharyngitis symptoms, and fatigue. The thyroid may be slightly enlarged, and is firm and painful to palpation. Subacute thyroiditis is thought to be due to a sequela of an upper respiratory viral infection that involves the thyroid gland.

About 50% of patients with subacute thyroiditis have an initial thyrotoxic phase due to unregulated release of preformed thyroid hormone from damaged thyroid follicular cells (24). Therefore, early in the course of the disease, patients may have clinical findings of thyrotoxicosis, although this is often mild. The serum TSH level is suppressed, and the free T_4 level may be elevated preferentially to the total T_3 level, in contrast to other endogenous forms of thyrotoxicosis, although there is substantial overlap among the etiologies (618). In addition to laboratory evidence of thyrotoxicosis, the erythrocyte sedimentation rate or C-reactive protein (CRP) is elevated, and mild

anemia and elevation of the white blood count (wbc) are common. Up to 25% of patients have low concentrations of anti-thyroid antibodies (24,619,620). RAIU is low, as is uptake on a thyroid scintigram. Thyroid ultrasonography shows diffuse heterogeneity, focal hypoechoic areas, and decreased or normal color-flow Doppler, rather than the enhanced flow characteristic of GD (621,622). A biopsy of the thyroid gland is not usually necessary in subacute thyroiditis. However, if a biopsy is performed due to uncertainty of the diagnosis, its result shows granulomatous infiltrate and giant cells, consistent with a viral infection (24).

The thyrotoxic phase usually lasts 3-6 weeks, ending when the thyroid stores of preformed hormone are depleted. About 30% of patients subsequently enter a hypothyroid phase that can last up to 6 months. Thyroid pain and the elevated ESR have usually resolved by this time, and the predominant clinical features are those of hypothyroidism with a small nontender goiter. Most patients become euthyroid again within 12 months of disease onset, although 5-15% have persistent hypothyroidism (24,620,621). In addition, recurrence rates of 1-4% have been reported (24,620,623).

■ **RECOMMENDATION 117**

Patients with mild symptomatic subacute thyroiditis should be treated initially with beta-adrenergic-blocking drugs and nonsteroidal anti-inflammatory agents. Corticosteroids should be used instead of nonsteroidal anti-inflammatory agents when patients fail to respond, or present initially with moderate to severe pain and/or thyrotoxic symptoms. **Strong recommendation, low-quality evidence.**

Subacute thyroiditis is treated with beta-blockers and anti-inflammatory therapy. Beta-blockers are used as needed to control thyrotoxic symptoms. Nonsteroidal anti-inflammatory agents (NSAIDs) provide pain relief in patients with mild symptoms, and should be considered first-line therapy. With NSAIDs, the median time for resolution of pain is 5 weeks (range 1-20 weeks) (24). Patients who fail to respond to full doses of NSAIDs over several days should be treated instead with corticosteroid therapy. Standard recommendations are to use 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 found that patients treated with corticosteroids at similar doses 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 (24). A more recent study reported that a lower initial daily dose of 15 mg of prednisolone, with tapering by 5 mg every two weeks, was effective. However, 20% of patients required longer than 8 weeks to discontinue the glucocorticoid (624). 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. ATDs have no role in the treatment of subacute thyroiditis.

[W2] Painless thyroiditis

Painless or silent thyroiditis classically presents with the same triphasic course described for subacute thyroiditis, but with no prodrome, neck pain, or elevated ESR, white blood cell count, or CRP (625). The postpartum period is the most common time when painless thyroiditis is seen, but painless thyroiditis can also occur in nonpregnant

women and in men. Painless thyroiditis has been described in some types of drug-induced thyroid dysfunction, including that associated with lithium or cytokine therapy. Postpartum and drug-induced thyroiditis are discussed in detail in sections [T4] and [X], respectively. A small nontender goiter is common in all types of painless thyroiditis.

The thyrotoxic phase occurs in 5-20% of patients and typically lasts 3-4 months. The hypothyroid phase is more common, or at least is recognized more often, lasting up to 6 months. Normal thyroid function is reestablished by 12 months in most patients, but 10-20% have persistent hypothyroidism. Recurrence rates are about 5-10%, but may be higher in Japan, with one Japanese study reporting a long-term recurrence rate of 65% (626). Recurrences are managed in the same manner as the initial occurrence, but rare patients with multiple recurrences have opted for surgery or RAI ablation of the gland following recovery from the thyrotoxic phase (626).

Painless thyroiditis is probably an autoimmune disease manifested by positive anti-TPO antibodies in about 50% of patients and findings of lymphocytic infiltration on pathology (626,627). During the thyrotoxic phase, the serum TSH level is suppressed and free T_4 levels are elevated, often out of proportion to T_3 levels. Patients with painless thyroiditis have a low RAIU and low uptake on a thyroid scintigram during the thyrotoxic phase, and ultrasound often shows inhomogeneous hypoechogenic texture with decreased blood flow. These tests and the absence of TRAb antibodies help distinguish painless thyroiditis from GD (628).

■ **RECOMMENDATION 118**

Patients with symptomatic thyrotoxicosis due to painless thyroiditis should be treated with beta-adrenergic-blocking drugs to control symptoms. **Strong recommendation, low-quality evidence.**

Beta-adrenergic blockers can be used to treat thyrotoxic symptoms in patients with painless thyroiditis, but ATDs 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 (629), but they should be reserved only for more severe cases.

[W3] Acute thyroiditis

■ **RECOMMENDATION 119**

Acute thyroiditis should be treated with antibiotics and surgical drainage as determined by clinical judgement. Beta blockers may be used to treat symptoms of thyrotoxicosis. **Strong recommendation, low-quality evidence.**

Patients with acute thyroiditis (also referred to as suppurative thyroiditis or thyroid abscess) are generally euthyroid. However, on occasion, the condition presents as destructive thyroiditis with thyrotoxicosis (630). Ultrasound or CT examinations are usually diagnostic, showing hypoechoic lesions in and around the affected thyroid lobe, destruction of the lobe, and abscess formation. However, early in the process, radiologic examination may be nonspecific, often leading to the erroneous diagnoses of subacute thyroiditis (631). 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 ATDs.

[W4] Palpation thyroiditis

In 1975, Carney et al described a nonspecific multifocal granulomatous folliculitis in thyroid glands removed at surgery for thyroid-related or unrelated conditions (632). They named this pathologic entity "palpation thyroiditis," concluding that it was due to palpation of the thyroid gland at surgery. It was generally thought to be of little clinical importance, except for rare case reports of patients who developed thyrotoxicosis following manipulation of the thyroid gland during surgery (633-636). However, a recent study suggested that the rate of transient overt or subclinical thyrotoxicosis following parathyroid surgery may be as high as 30%, although there was likely ascertainment bias because not all patients had post-operative TSH levels measured (637). There are no data on treatment of palpation thyroiditis, although the use of beta blockers for symptomatic thyrotoxicosis seems reasonable.

[X] How should other causes of thyrotoxicosis be managed?

Tables 16 and 17 summarize drug-associated and unusual causes of thyrotoxicosis.

■ **RECOMMENDATION 120**

Patients taking medications known to cause thyrotoxicosis, including interferon- α, IL-2, tyrosine kinase inhibitors, and lithium, should be monitored clinically and biochemically at 6-month intervals for the development of thyroid dysfunction. Patients who develop thyrotoxicosis should be evaluated to determine etiology and treated accordingly. **Strong recommendation, low-quality evidence.**

[X1] Interferon- α and interleukin-2

Interferon-α (IFN-α) and interleukin-2-treated patients are at increased risk for developing thyrotoxicosis, especially those with pre-existing thyroid autoimmunity. A recent study including 1233 patients who were euthyroid at baseline found that 79 (6.4%) patients developed a biphasic thyroiditis and an additional 57 (4.6%) patients developed a suppressed TSH value (638). The latter group included 33 patients with mild TSH suppression and 24 with a TSH value < 0.1 mU/L, among whom 11 had free T_4 elevation and 5 required antithyroid drug therapy (638). Thyrotoxicosis in patients treated with IFN-α can be due to either painless thyroiditis or GD (639). In a review of published cases from 8 series, 69% of 49 patients with IFN-α-associated thyrotoxicosis, for whom an etiology was identified, were found to have GD, based on either positive TRAb titers or requirement for a prolonged course of ATDs (640). An earlier literature review found that 2.4% of 1664 patients treated with IFN-α therapy for hepatitis C infection developed thyrotoxicosis, although the specific etiology was not consistently identified (641).

[X2] Tyrosine Kinase Inhibitors

The tyrosine kinase inhibitors sunitinib (642-647), sorafenib (648-650), and nilotinib (651) have each been associated with a transient thyrotoxicosis due to destructive thyroiditis. One study of 69 patients treated with sorafenib for metastatic renal cell carcinoma found that 11 (16%) developed transient thyroiditis followed by hypothyroidism (649). Another study found that 6 of 31 (19.3%) receiving sunitinib therapy for metastatic renal cell carcinoma developed thyrotoxicosis, including one case of thyroid storm (644).

[X3] Lithium

Patients taking lithium for bipolar disorder are at a high risk of developing thyroid dysfunction, including both hypothyroidism, and to a lesser extent, thyrotoxicosis (652). Two published series have identified the development of thyrotoxicosis in 0.6% and 3.0% of patients, respectively (653,654). An epidemiological study of hyperthyroidism occurring over a 3-year period in Denmark identified lithium-associated thyrotoxicosis as the etiology in 0.7% of all cases (432). A case series of 24 patients with lithium-associated thyrotoxicosis identified GD in 12 (50%), painless thyroiditis in two patients, toxic multinodular goiter in 3 patients, and no identified etiology in 7 patients (655). Another more recent series found that 1.4% of referrals to a thyroid clinic over a 12-year period were for lithium related thyrotoxicosis (656). Patients in this series had been taking lithium for a median duration of 6 years (range 0.6-25 years), and 87% were women. Diagnostic evaluation found that 11 (47.8%) had GD, 9 (39%) had painless thyroiditis, 2 had toxic MNG, and one patient had subacute thyroiditis (656). A smaller series described three cases of GD occurring in patients receiving lithium (657). In a

retrospective review of 100 cases of thyroiditis and 400 cases of GD occurring at a single medical center, 6 cases of painless thyroiditis had a history of recent lithium exposure, representing a nearly 5-fold increase compared to cases of lithium exposure in patients with GD (19).

[X4] TSH-secreting pituitary tumors

■ **RECOMMENDATION 121**

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 and total T_3 concentrations, generally associated with a pituitary tumor on MRI or CT, and the absence of a family history or genetic testing consistent with thyroid hormone resistance. **Strong recommendation, low-quality evidence.**

TSH-secreting pituitary adenomas are rare tumors and represent an even rarer cause of hyperthyroidism. Recent data from the Swedish registry reported an incidence of 0.15 per 1 million inhabitants with a prevalence of 2.8 cases per million (658). After excluding laboratory interference with either the free T_4 or TSH assay, as may occur with T_4 antibodies and heterophilic antibodies, respectively, 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. Finally, a response to somatostatin analog therapy with clinical improvement lends support to the diagnosis of a TSH adenoma in cases in which diagnostic uncertainty persists. Although most TSH-secreting pituitary adenomas only secrete TSH, co-secretion of prolactin or growth hormone is possible and should be assessed concurrently **along with assessment of the pituitray-adrenal axis and pituitary-gonadal axes.**

Technical remarks: Genetic testing for thyroid hormone resistance is commercially available and may be useful in equivocal cases, especially in those patients without family members available for thyroid function testing. Calculation of the molar alpha subunit/TSH ratio can be accomplished by dividing the alpha subunit concentration (ng/mL) by TSH (mU/L) and multiplying by 10. A ratio greater than 1 favors a TSH-secreting pituitary adenoma.

Pituitary surgery is generally the mainstay of therapy for TSH-producing pituitary tumors. In a recent series of 68 patients undergoing transsphenoidal surgery, 75% normalize thyroid function after surgery, 58% normalized both pituitary imaging and TSH hypersecretion, 9% developed new deficiencies, and 3% experienced tumor recurrence (659). The patient should be made euthyroid preoperatively. Long-term ATD therapy and other measures directed at the thyroid, such as RAI or thyroidectomy, are generally avoided due to theoretical concerns of tumor growth. 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 (43). A reduction in tumor size has been observed in 20%–50% of patients treated with octreotide (43,660), but less impressive results have been obtained with bromocriptine therapy (660). However, presurgical medical treatment did not significantly improve surgical outcome (63% vs 57% had negative tumor imaging after surgery) (659). In a recent case series of 7 patients treated with octreotide without prior surgery, mean free T_4 and T_3 levels were reduced by nearly 50% in the first three months of therapy and 6 of 7 patients experienced tumor volume reduction (661).

Sterotactic or conventional radiotherapy has also been used in cases that prove refractory to medical therapy. Radiotherapy controlled thyroid hypersecretion in 37% of patients treated with this modality, but hypopituitarism occurred in 32% of those treated (659). For patients with TSH-producing adenomas who are considered poor surgical candidates, primary medical therapy with octreotide can be considered (661). Patients who fail to respond to pituitary surgery and somatostatin analog therapy or have tumor enlargement despite these measures are sometimes treated with radiation therapy.

■ **RECOMMENDATION 122**

Patients with TSH-secreting pituitary adenomas should undergo surgery performed by an experienced pituitary surgeon. **Strong recommendation, low-quality evidence.**

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 (43).

[X5] Struma ovarii

■ **RECOMMENDATION 123**

Patients with struma ovarii should be treated initially with surgical resection following preoperative normalization of thyroid hormones. **Strong recommendation, low-quality evidence.**

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 (662) 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 (663). The diagnosis should be considered in any thyrotoxic patient with a very low or absent RAI uptake over the eutopic thyroid gland. Other conditions that present with this constellation of findings include various forms of thyroiditis, factitious thyrotoxicosis, and iodine-induced hyperthyroidism. In struma ovarii, the RAI is concentrated in the pelvic region over the teratoma. Cosynchronous primary thyroid cancer occurred in 9% of patients in one series of 68 patients identified in the SEER database (664). Treatment of struma ovarii generally involves surgical removal, performed both to cure the hyperthyroidism and to eliminate

the risk of untreated ectopic thyroid cancer. Preoperative treatment with beta-adrenergic-blocking agents and ATDs is warranted to restore euthyroidism before surgery.

Technical remarks: In cases of suspected metastatic malignant struma ovarii, RAI 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.

[X6] Choriocarcinoma

■ **RECOMMENDATION 124**

Treatment of hyperthyroidism due to choriocarcinoma should include both MMI and treatment directed against the primary tumor. **Strong recommendation, low-quality evidence.**

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 (665-668). This cross-stimulation only occurs at very high levels of hCG, since hCG is only a weak agonist for the TSH receptor. Therefore, patients with testicular choriocarcinoma presenting with overt thyrotoxicosis may have widely metastatic disease at presentation (667,668). Treatment of hyperthyroidism due to choriocarcinoma involves both treatment directed against the primary tumor and ATDs.

[X7] 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 hormone (669). Historically, accidental thyroid hormone ingestion has occurred as a result of eating meat contaminated with animal thyroid tissue (‘‘hamburger thyrotoxicosis’’) (670).

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 RAI uptake. In a patient who has circulating antithyroglobulin antibodies that artifactually render the serum thyroglobulin undetectable in immunometric assays, the distinction between painless thyroiditis and factitious thyrotoxicosis can be difficult. In both situations there will be elevated levels of T_4, a high T_4/T_3 ratio (with exogenous levothyroxine), a small thyroid, and a low thyroidal RAI uptake. Thyroid ultrasound may be helpful, as the thyroid has a heterogeneous echotexture and is normal-sized or slightly enlarged in painless thyroiditis, while it is small with a normal echotexture in an otherwise normal individual who is ingesting thyroid hormone surreptitiously. Fecal levothyroxine has been measured as a means of distinguishing surreptitious use of thyroid hormone from painless thyroiditis (54). A disproportionately elevated T_3 level suggests that the patient may be ingesting liothyronine or a combination T_4/T_3 preparation.

Severe thyrotoxicosis and rarely, thyroid storm, have been reported following thyroid hormone overdose or poisoning. Treatment with Cholestyramine (671) and charcoal hemoperfusion (672) have been used in this circumstance.

[X8] 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 (673). In general, functioning metastasis are treated with RAI with the addition of ATDs as needed for persistent hyperthyroidism. Recombinant human TSH should be avoided in these patients. Patients with massive metastatic FC may also exhibit T_3 thyrotoxicosis, most likely due to increased conversion of T_4 to T_3 by tumor expressing high type 1 and type 2 deiodinase activities (674). Thus, occasional measurement of serum T_3 in addition to FT_4 and TSH is recommended in patients with a large metastatic tumor burden, particularly if FT_4 decreases on fixed doses of levothyroxine.