AMERICAN THYROID ASSOCIATION
FOUNDED 1923
www.thyroid.org

HYPERTHYROIDISM

American Thyroid Association Task Force Updates Treatment Guidelines for Hyperthyroidism

FULL JOURNAL TITLE

Ross, D et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis. Ross, Burch, et al., Thyroid. Oct 2016, 26(10): 1343-1421.

American Thyroid Association Task Force Updates Treatment Guidelines for Hyperthyroidism

Kimberly Dorris, Executive Director/CEO
Graves' Disease and Thyroid Foundation

A task force organized by the American Thyroid Association (ATA) has updated the organization›s *"Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis."* The Guidelines, published in *Thyroid*, a peer-reviewed journal from Mary Ann Liebert, Inc., publishers and the official journal of the ATA, are available free on the *Thyroid* website.

Thyrotoxicosis refers to having excessive levels of thyroid hormone in the body and can occur because of hyperthyroidism (overactive thyroid), inflammation of the thyroid, ingesting too much thyroid hormone from external sources, or other causes. Graves' disease is the most common cause of hyperthyroidism.

The task force was chaired by Dr. Douglas Ross (Massachusetts General Hospital, Boston, MA) and included Dr. Henry Burch (Walter Reed National Military Center, Bethesda, MD), Dr. David Cooper (Johns Hopkins Medicine in Baltimore, MD), Dr. M. Carol Greenlee (Western Slope Endocrinology Grand Junction, CO), Dr. Peter Laurberg (Aalborg University, Aalberg, Denmark), Dr. Ana Luiza Maia (Federal University of Rio Grande do Sul, Porto Alegre, Brazil), Dr. Scott Rivkees (University of Florida College of Medicine, Gainsville, FL), Dr. Mary Samuels (Oregon health and Science University, Portland, Oregon), Dr. Julie Ann Sosa (Duke University School of Medicine, Durham, North Carolina), Dr. Marius Stan (Mayo Clinic, Rochester, MN) and Dr. Martin Walter (University Hospital Bern, Switzerland). Drs. Cooper and Greenlee are GDATF Physician Advisory Board members and Dr. Rivkees is a GDATF newsletter contributor. The new guidelines include 124 evidence-based recommendations.

Much of the information in the 2011 guidance has been retained, including the following:

- Critical information on diagnostic testing, as the specific diagnosis will determine the available treatment options. For hyperthyroidism due to Graves' disease, treatment options include antithyroid medications (ATDs), radioiodine therapy (RAI) and thyroidectomy. However, none of these options are recommended for thyroiditis, an inflammation of the thyroid; rather, treatment usually involves the prescription of beta blockers (medications which slow the heart rate), with additional measures recommended depending on the type of thyroiditis. For overactive nodules, RAI or thyroidectomy are commonly used, with ATDs less frequently prescribed.

- A discussion of treatment options for patients living with thyroid eye disease; antithyroid drugs or surgery are still recommended over RAI for patients with active and moderate-to-severe or sight-threatening eye involvement.

- An emphasis on the importance of incorporating the patient's values and wishes into the final treatment decision.

ATA Task Force Updates Treatment Guidelines for Hyperthyroidism, continued

The guidance notes the increasing popularity in the United States of ATDs for the treatment of Graves' disease. ATDs are the preferred treatment option in Europe, Latin America, and Japan. Although RAI remains the most common treatment option in the USA, this option has been used with decreasing frequency over the last 20 years.

The updated guidance includes a review of newly published research studies and how the findings impact clinical care decisions; key areas of interest are discussed below.

Diagnostic Testing. Although both antibody testing and a radioactive uptake test can distinguish Graves' disease from other sources of thyrotoxicosis, a recent study found that the use of antibody testing resulted in reduced costs and a quicker time to diagnosis. In addition, physicians have discovered that biotin, a supplement frequently touted for its benefits to hair and skin, can interfere with thyroid function tests. For patients who are taking biotin and are found to have low TSH and/or high T_4, the guidance recommends discontinuing the supplement and retesting in two days.

Treatment with Radioactive Iodine. For individuals at risk of complications due to worsening hyperthyroidism (specifically the elderly and those with other medical conditions), consideration should be given to re-starting ATDs 3-7 days following RAI treatment. For women who are breast-feeding, the new guidance recommends delaying RAI treatment until three months after lactation stops. The new guidance also mentions cancer risk, noting that, *"A recent meta-analysis found no increase in the overall cancer risk after RAI treatment for hyperthyroidism; however, a trend towards increased risk of thyroid, stomach and kidney cancer was seen, requiring further research."*

Treatment with Antithyroid Medications. The new guidance includes an expanded section on the initial dosing for ATDs, based on the severity of hyperthyroidism. The goal is to prescribe a high enough dose to normalize thyroid function, while minimizing the risk of side effects. Although methimazole can be taken once a day, split dosing (for example, taking 15 mg twice per day instead of 30 mg once per day) may be more effective for patients with severe hyperthyroidism.

The new guidance also goes into greater detail on potential side effects with antithyroid medications. Minor reactions include rash and itching; more serious reactions are rare, but can include damage to the liver and a severe reduction in white blood cell count. The vast majority of reactions occur within the first 90 days of stopping or re-starting the medications. The one exception is vasculitis, a dangerous inflammation of blood vessels that is more common with increased duration of ATD dosing (More risk with PTU than Tapazole). Children and patients of Asian ethnicity are at particular risk for vasculitis.

Monitoring recommendations have changed slightly, with thyroid function testing now recommended at 2-6 weeks instead of four weeks. As with the 2011 guidance, the new document notes that, *"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 thyroid levels have stabilized, a dose reduction of 30-50% is recommended, with testing repeated in 4-6 weeks.

The 2016 guidelines place new emphasis on antibody testing, noting that ATDs should be discontinued if TSH and TRAb are normal. *"TRAb assessment at the end of the course of ATD therapy is a useful method of dividing patients into two 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. In the group with elevated TRAb, relapse rates approach 80-100%, while in the latter group, relapse rates are in the 20-30% range."* Even in patients with negative TRAb, relapses can still occur, so thyroid levels *"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."*

ATA Task Force Updates Treatment Guidelines for Hyperthyroidism, continued

Additional information is provided regarding the long-term use of antithyroid medications for patients with persistently elevated TRAb, particularly those who have *"mild stable disease on a low dose of MMI."* Recent studies have found long-term use of ATDs to be safe, and one study found that this approach was superior to RAI in terms of avoiding thyroid eye disease, maintaining euthyroidism, and stabilizing weight.

The new guidance also discusses the possible use of potassium iodide as "adjunct" to ATD therapy; recent studies indicate that this may result in more rapid control of hyperthyroidism with fewer side effects.

Treatment with Thyroidectomy. The new guidance notes that the availability of local surgical expertise affects the decision to move forward with thyroidectomy. The use of a high-volume surgeon results in a reduced risk of complications, reduced hospital stays, and reduced costs. Low blood calcium due to damaged parathyroid glands is a common complication of thyroid surgery and can cause symptoms such as tingling and muscle spasms. Although the prior guidelines recommended testing calcium levels following thyroidectomy, recent research has demonstrated a value in testing calcium levels prior to surgery; advance supplementation should be considered in patients at increased risk for hypoparathyroidism.

Following surgery, the new guidance recommends testing Free T_4 in patients with previously suppressed TSH in order to determine the correct dosing of thyroid hormone. In addition, the new guidance stresses the importance of communication among the patient's entire medical team – both prior to surgery and during the postoperative period.

Thyroid Storm. The new guidelines include an expanded section on the diagnosis and management of thyroid storm, a life-threatening emergency that can occur in patients with untreated or inadequately treated hyperthyroidism. Thyroid storm can also occur in patients who abruptly stop ATDs, experience an acute nonthyroidal illness, or undergo surgery or childbirth without adequate control of hyperthyroidism. Treatment of thyroid storm can include the use of ATDs (PTU is preferred over methimazole, as it can prevent the conversion of T_4 into T_3), steroids, beta blockers, iodine, and more extreme measures such as plasma exchange and emergency surgery.

Children and Graves' disease. The new guidance tweaks the time frames for monitoring thyroid levels for children taking antithyroid drugs. Testing is now recommended 2-6 weeks after starting antithyroid medications with a subsequent follow up 4-6 weeks later, and then at 2-3 month intervals. The new guidance also mentions the need to be vigilant for weight gain in children taking ATDs, with nutritional consultation considered for children experiencing excessive weight gain.

Subclinical hyperthyroidism. This section has been expanded to include a discussion regarding the controversy over whether to treat subclinical hyperthyroidism (SH). Patients with SH have TSH levels below the normal range, but normal range T_3 and T4. Although the research has produced conflicting results, some studies have found an increased risk of cardiovascular issues, osteoporosis, cognitive decline, and overall mortality for patients with untreated subclinical hyperthyroidism. The 2011 guidance noted that treatment of subclinical hyperthyroidism should be "strongly considered" 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."* The new guidance now lists treatment as recommended for these individuals.

Graves' disease and pregnancy. The 2016 guidance includes a significantly expanded section on Graves' disease and pregnancy. Physicians are advised to initiate a discussion of future pregnancy plans with patients of child-bearing age: *"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."*

ATA Task Force Updates Treatment Guidelines for Hyperthyroidism, continued

The 2016 guidance includes an expanded discussion of the risk of birth defects with methimazole and PTU. PTU has long been the mainstay of anti-thyroid drug therapy for women in the first trimester of pregnancy, as methimazole has been associated with an increased risk of birth defects. However, new research has identified an increased risk of birth defects with PTU as well, although these tend to be less serious than those associated with methimazole. Options for women with Graves' who are taking methimazole and planning a future pregnancy include switching to PTU while trying to conceive; switching to PTU after a pregnancy is confirmed; choosing definitive therapy prior to trying to conceive; or withdrawing antithyroid drugs when pregnancy is confirmed. If antithyroid medications are withdrawn, the guidance recommends checking levels weekly throughout the first trimester, and then monthly thereafter. It must be noted that while discontinuation of ATDs at this point in pregnancy is discussed there remains a need for additional research in this area. During the second trimester, patients can remain on PTU or switch back to methimazole.

If large doses of antithyroid medications are required for the patient to remain euthyroid, definitive therapy is the preferred option. For those who choose to remain on antithyroid medications while trying to conceive, patients are advised to test for pregnancy *"within the first days after a missed or unusually light menstrual period"* and to contact their endocrinologist or managing physician within 24 hours of a positive test.

For women who are pregnant and have not yet achieved euthyroidism, treatment with propranolol or metoprolol is considered safe for "short periods of time" to help alleviate symptoms such as tremors and rapid heart rate.

The new guidance also mentions the short-term increase in antibodies that can occur following treatment with RAI. "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. 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."

Guidelines for antibody testing in pregnancy have been updated, with testing now recommended during the first trimester and then again at 18-22 weeks if levels are elevated.

For women with severe disease, the new guidelines recommend frequent monitoring of maternal thyroid function as well as "non-invasive assessment of fetal thyroid function (e.g. fetal heart rate, bone maturity, and fetal goiter on ultrasound)".

ADDITIONAL UPDATES:

- Iodine could potentially be a treatment option for patients who are unable to tolerate ATDs and who are not candidates for surgery or RAI; this approach might also be effective in patients who have had one failed RAI.

- The new guidance discusses the use of ethanol and radiofrequency for ablation of overactive nodules, options that have been used primarily outside the United States. The guidance notes that these approaches "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."

- For patients taking medications known to potentially cause thyrotoxicosis (such as lithium or amiodarone), thyroid function testing is recommended at 6 month intervals.

In conclusion, it's important to note that these guidelines are just that – guidelines. As the task force members note, *"It is not the intent of these guidelines to replace clinical judgment, individual decision making, or the wishes of the patient*

ATA Task Force Updates Treatment Guidelines for Hyperthyroidism, continued

or family. Rather, each recommendation should be evaluated in light of these elements in order that optimal patient care is delivered." If your own provider's recommendations differ from what is outlined here, these guidelines should be used as a starting point for an open discussion. Each patient has a unique experience with thyroid dysfunction as well as a unique medical and family history, and any treatment recommendations should be tailored accordingly.

Would you like to review the guidance in full? Please visit the Professional Guidelines page of the American Thyroid Association's website at http://www.thyroid.org/professionals/ata-professional-guidelines/.