Supplementary Data

1. Information Pertinent to This Publication Regarding American Thyroid Association Clinical Practice Guidelines and American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice

American Thyroid Association Clinical Practice Guidelines

The American Thyroid Association (ATA) develops Clinical Practice Guidelines to provide guidance and recommendations for particular practice areas concerning thyroid disease and thyroid cancer. The guidelines are not inclusive of all proper approaches or methods, or exclusive of others. The guidelines do not establish a standard of care and specific outcomes are not guaranteed.

Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances. A guideline is not intended to take the place of physician judgment in diagnosing and treatment of particular patients.

The ATA develops guidelines based on the evidence available in the literature and the expert opinion of the task force in the recent timeframe of the publication of the guidelines. Management issues have not been and cannot be comprehensively addressed in randomized trials; therefore, the evidence cannot be comprehensive. Guidelines cannot always account for individual variation among patients. Guidelines cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Therefore, the American Thyroid Association considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the treating physician and health care professionals with the full consideration of the individual patient's clinical history and physical status. In addition, the guideline concerns the therapeutic interventions used in clinical practice and do not pertain to clinical trials. Clinical trials are a separate matter, designed to research new and novel therapies, and the guidelines are not necessarily relevant to their purpose.

Guideline development includes an identification of areas for future study and research, indicating the focus for future investigational therapy; based on the findings reviewed and synthesized from the latest literature.

American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice

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

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

2. List of Hypothyroidism Guideline Recommendations

Recommendation 1: Anti-peroxidase antibody (TPOAb) measurements should be considered when evaluating patients with subclinical hypothyroidism. **Grade B, BEL 1**

Recommendation 2: TPOAb measurement should be considered in order to identify autoimmune thyroiditis when nodular thyroid disease is suspected to be due to autoimmune thyroid disease. **Grade D, BEL 4**

Recommendation 3: TPOAb measurement should be considered when evaluating patients with recurrent miscarriage, with or without infertility. **Grade A, BEL 2**

Recommendation 4: Measurement of anti–TSH receptor antibodies (TSHRAbs) using a sensitive assay should be considered in hypothyroid pregnant patients with a history of Graves' disease who were treated with radioactive iodine or thyroidectomy prior to pregnancy. This should be initially done either at 20–26 weeks of gestation or during the first trimester and if they are elevated again at 20–26 weeks of gestation. **Grade A, BEL 2**

Recommendation 5: Clinical scoring systems should not be used to diagnose hypothyroidism. **Grade A, BEL 1**

Recommendation 6: Tests such as clinical assessment of reflex relaxation time, cholesterol, and muscle enzymes should not be used to diagnose hypothyroidism. **Grade B, BEL 2**

Recommendation 7: Apart from pregnancy, assessment of serum free T_4 should be done instead of total T_4 in the evaluation of hypothyroidism. An assessment of serum free T_4 includes a free T_4 index or free T_4 estimate and direct immunoassay of free T_4 without physical separation using anti-T_4 antibody. **Grade A, BEL 1**

Recommendation 8: Assessment of serum free T_4, in addition to TSH, should be considered when monitoring L-thyroxine therapy. **Grade B, BEL 1**

Recommendation 9: In pregnancy, the measurement of total T_4 or a free T_4 index, in addition to TSH, should be done to assess thyroid status. Because of the wide variation in the results of different free T_4 assays, direct immunoassay measurement of free T_4 should only be employed when method-specific and trimester-specific reference ranges for serum free T_4 are available. **Grade B, BEL 2**

Recommendation 10: Serum total T_3 or assessment of serum free T_3 should not be done to diagnose hypothyroidism. **Grade A, BEL 2**

Recommendation 11: TSH measurements in hospitalized patients should be done only if there is an index of suspicion for thyroid dysfunction. **Grade A, BEL 2**

Recommendation 12: In patients with central hypothyroidism, assessment of free T_4 or free T_4 index, not TSH, should be done to diagnose and guide treatment of hypothyroidism. **Grade A, BEL 1**

Recommendation 13: Patients being treated for established hypothyroidism should have serum TSH measurements done at 4–8 weeks after initiating treatment or after a change in dose. Once an adequate replacement dose has been determined, periodic TSH measurements should be done after 6 months and then at 12-month intervals, or more frequently if the clinical situation dictates otherwise. **Grade B, BEL 2**

Recommendation 14.1: The reference range of a given laboratory should determine the upper limit of normal for a third generation TSH assay. The normal TSH reference range changes with age. If an age-based upper limit of normal for a third generation TSH assay is not available in an iodine sufficient area, an upper limit of normal of 4.12 should be considered. **Grade A, BEL 1**

Recommendation 14.2: In pregnancy, the upper limit of the normal range should be based on trimester-specific ranges for that laboratory. If trimester-specific reference ranges for TSH are not available in the laboratory, the following upper normal reference ranges are recommended: first trimester, 2.5 mIU/L; second trimester, 3.0 mIU/L; third trimester, 3.5 mIU/L. **Grade B, BEL 2**

Recommendation 15: Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine. **Grade B, BEL 1**

Recommendation 16: Treatment based on individual factors for patients with TSH levels between the upper limit of a given laboratory's reference range and 10 mIU/L should be considered particularly if patients have symptoms suggestive of hypothyroidism, positive TPOAb or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases. **Grade B, BEL 1**

Recommendation 17: In patients with hypothyroidism who are not pregnant, the target range should be the normal range of a third generation TSH assay. If an upper limit of normal for a third generation TSH assay is not available, in iodine-sufficient areas an upper limit of normal of 4.12 mIU/L should be considered and if a lower limit of normal is not available, 0.45 mIU/L should be considered. **Grade B, BEL 2**

Recommendation 18: In patients with hypothyroidism who are pregnant, the target range for TSH should be based on trimester-specific ranges for that laboratory. If trimester-specific reference ranges are not available in the laboratory, the following upper-normal reference ranges are recommended: first trimester, 2.5 mIU/L; second trimester, 3.0 mIU/L; and third trimester, 3.5 mIU/L. **Grade C, BEL 2**

Recommendation 19.1: Treatment with L-thyroxine *should be considered* in women of childbearing age with serum TSH levels between 2.5 mIU/L and the upper limit of normal for a given laboratory's reference range if they are in the first trimester of pregnancy or planning a pregnancy including assisted reproduction in the immediate future. Treatment with L-thyroxine should be considered in women in the second trimester of pregnancy with serum TSH levels between 3.0 mIU/L and the upper limit of normal for a given laboratory's reference range, and in women in the third trimester of pregnancy with serum TSH levels between 3.5 mIU/L and the upper limit of normal for a given laboratory's reference range. **Grade B, BEL 2**

Recommendation 19.2: Treatment with L-thyroxine *should be considered* in women of childbearing age with normal serum TSH levels when they are pregnant or planning a pregnancy, including assisted reproduction in the immediate future, if they have or have had positive levels of serum TPOAb, particularly when there is a history of miscarriage or past history of hypothyroidism. **Grade B, BEL 2**

Recommendation 19.3: Women of childbearing age who are pregnant or planning a pregnancy, including assisted reproduction in the immediate future, *should be treated* with L-thyroxine if they have or have had positive levels of serum TPOAb and their TSH is greater than 2.5 mIU/L. **Grade B, BEL 2**

Recommendation 19.4: Women with positive levels of serum TPOAb or with a TSH greater than 2.5 mIU/L who are not being treated with L-thyroxine should be monitored every 4 weeks in the first 20 weeks of pregnancy for the development of hypothyroidism. **Grade B, BEL 2**

Recommendation 20.1.1: Universal screening is not recommended for patients who are pregnant or are planning pregnancy, including assisted reproduction. **Grade B, BEL 1**

Recommendation 20.1.2: "Aggressive case finding," rather than universal screening, should be considered for patients who are planning pregnancy. **Grade C, BEL 2**

Recommendation 20.2: Screening for hypothyroidism should be considered in patients over the age of 60. **Grade B, BEL 1**

Recommendation 21: "Aggressive case finding" should be considered in those at increased risk for hypothyroidism. **Grade B, BEL 2**

Recommendation 22.1: Patients with hypothyroidism should be treated with L-thyroxine monotherapy. **Grade A, BEL 1**

Recommendation 22.2: The evidence does not support using L-thyroxine and L-triiodothyronine combinations to treat hypothyroidism. **Grade B, BEL 1**

Recommendation 22.3: L-thyroxine and L-triiodothyronine combinations should not be administered to pregnant women or those planning pregnancy. **Grade B, BEL 3**

Recommendation 22.4: There is no evidence to support using desiccated thyroid hormone in preference to L-thyroxine

monotherapy in the treatment of hypothyroidism and therefore desiccated thyroid hormone should not be used for the treatment of hypothyroidism. **Grade D, BEL 4**

Recommendation 22.5: 3,5,3′-triiodothyroacetic acid (TRIAC; tiratricol) should not be used to treat primary and central hypothyroidism due to suggestions of harm in the literature. **Grade C, BEL 3**

Recommendation 22.6: Patients resuming L-thyroxine therapy after interruption (less than 6 weeks) and without an intercurrent cardiac event or marked weight loss may resume their previously employed full replacement doses. **Grade D, BEL 4**

Recommendation 22.7.1: When initiating therapy in young healthy adults with overt hypothyroidism, beginning treatment with full replacement doses should be considered. **Grade B, BEL 2**

Recommendation 22.7.2: When initiating therapy in patients older than 50–60 years with overt hypothyroidism, without evidence of coronary heart disease, an L-thyroxine dose of 50 μg daily should be considered. **Grade D, BEL 4**

Recommendation 22.8: In patients with subclinical hypothyroidism, initial L-thyroxine dosing is generally lower than what is required in the treatment of overt hypothyroidism. A daily dose of 25–75 μg should be considered, depending on the degree of TSH elevation. Further adjustments should be guided by clinical response and follow-up laboratory determinations including TSH values. **Grade B, BEL 2**

Recommendation 22.9: Treatment with glucocorticoids in patients with combined adrenal insufficiency and hypothyroidism should precede treatment with L-thyroxine. **Grade B, BEL 2**

Recommendation 23: L-thyroxine should be taken with water consistently 30–60 minutes before breakfast or at bedtime 4 hours after the last meal. It should be stored properly per product insert and not taken with substances or medications that interfere with its absorption. **Grade B, BEL 2**

Recommendation 24: In patients with central hypothyroidism, assessments of serum free T_4 should guide therapy and targeted to exceed the midnormal range value for the assay being used. **Grade B, BEL 3**

Recommendation 25.1: In patients with hypothyroidism being treated with L-thyroxine who are pregnant, serum TSH should be promptly measured after conception and L-thyroxine dosage adjusted, with a goal TSH of less than 2.5 mIU/L during the first trimester. **Grade B, BEL 2**

Recommendation 25.2: In patients with hypothyroidism being treated with L-thyroxine who are pregnant, the goal TSH during the second trimester should be less than 3 mIU/L and during the third trimester should be less than 3.5 mIU/L. **Grade C, BEL 2**

Recommendation 25.3: Maternal serum TSH (and total T_4) should be monitored every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation and L-thyroxine dosages adjusted as indicated. **Grade B, BEL 2**

Recommendation 26: In patients receiving L-thyroxine treatment for hypothyroidism, serum TSH should be remeasured within 4–8 weeks of initiation of treatment with drugs that decrease the bioavailability or alter the metabolic disposition of the L-thyroxine dose. **Grade A, BEL 1**

Recommendation 27: Apart from pregnant patients being treated with L-thyroxine for hypothyroidism, the evidence does not support targeting specific TSH values within the normal reference range. **Grade B, BEL 2**

Recommendation 28: Physicians who are not endocrinologists, but who are familiar with the diagnosis and treatment of hypothyroidism *should be able* to care for most patients with primary hypothyroidism. However, patients with hypothyroidism who fall into the following categories should be seen in consultation with an endocrinologist. These categories are (i) children and infants, (ii) patients in whom it is difficult to render and maintain a euthyroid state, (iii) pregnancy, (iv) women planning conception, (v) cardiac disease, (vi) presence of goiter, nodule, or other structural changes in the thyroid gland, (vii) presence of other endocrine disease such as adrenal and pituitary disorders, (viii) unusual constellation of thyroid function test results, and (ix) unusual causes of hypothyroidism such as those induced by agents that interfere with absorption of L-thyroxine, impact thyroid gland hormone production or secretion, affect the hypothalamic–pituitary–thyroid axis (directly or indirectly), increase clearance, or peripherally impact metabolism. **Grade C, BEL 3**

Recommendation 29: Thyroid hormones should not be used to treat symptoms suggestive of hypothyroidism without biochemical confirmation of the diagnosis. **Grade B, BEL 2**

Recommendation 30: Thyroid hormones should not be used to treat obesity in euthyroid patients. **Grade A, BEL 2**

Recommendation 31: There is insufficient evidence to support using thyroid hormones to treat depression in euthyroid patients. **Grade B, BEL 2**

Recommendation 32.1: Iodine supplementation, including kelp or other iodine-containing functional foods, should not be used in the management of hypothyroidism in iodine-sufficient areas. **Grade C, BEL 3**

Recommendation 32.2: Iodine supplementation in the form of kelp or other seaweed-based products should not be used to treat iodine deficiency in pregnant women. **Grade D, BEL 4**

Recommendation 33: Selenium should not be used to prevent or treat hypothyroidism. **Grade B, BEL 2**

Recommendation 34: Patients taking dietary supplements and nutraceuticals for hypothyroidism should be advised that commercially available thyroid-enhancing products are not a remedy for hypothyroidism and should be counseled about the potential side effects of various preparations particularly those containing iodine or sympathomimetic amines as well as those marked as "thyroid support" since they could be adulterated with L-thyroxine or L-triiodothyronine. **Grade D, BEL 4**