

primed

3:45 – 4:45 pm

Clinical Practice Guidelines for the Management of Thyroid Disorders

SPEAKER
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primed

Presenter Disclosure Information

The following relationships exist related to this presentation:

- ▶ James Hennessey, MD, FACP: No financial relationships to disclose.

Off-Label/Investigational Discussion

- ▶ In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Thyroid Nodules

Management of Thyroid Nodules

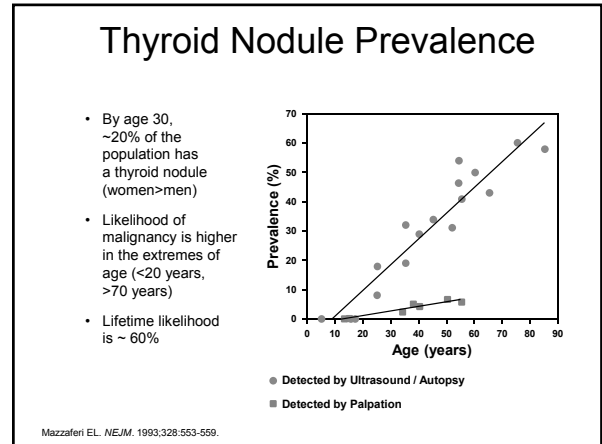
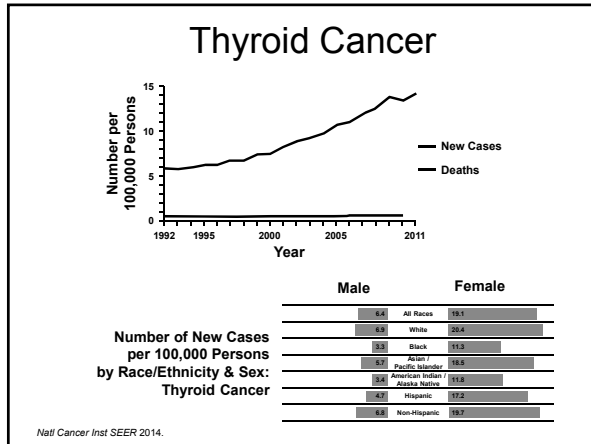
- Increasing incidence of thyroid cancer
- Evaluation of patients with thyroid nodules, use of imaging and indications for fine needle aspiration
- Managing nodules within a multinodular goiter
- Management of functioning nodules

Case 1

- A 48 year old man is in a motor vehicle accident and sustains a neck injury. A neck MRI is performed and is negative for cervical spine injury, but an incidental finding is noted of a 2 x 2 cm nodule in the right lobe of the thyroid. The patient has no family history of thyroid cancer and no history of radiation exposure.
- Physical exam is remarkable for right thyroid lobe prominence, but no discrete palpable thyroid nodules and no palpable lymph nodes.

Case 1-Questions

1. Which tests should be obtained?
2. Should additional imaging be ordered?
3. Should the nodule undergo fine needle aspiration?
4. What is the risk of malignancy?



Should a patient with a suspected thyroid nodule have an ultrasound?

- Thyroid sonography should be performed in all patients with known or suspected thyroid nodules

STRONG RECOMMENDATION
HIGH-QUALITY EVIDENCE

Haugen. ATA Nodule Guidelines Thyroid (in review) 2015.

What is the appropriate laboratory and imaging evaluation for patients with clinically or incidentally discovered thyroid nodules?

Serum TSH measurement

- Serum TSH should be measured during the initial evaluation.

STRONG RECOMMENDATION
MODERATE-QUALITY EVIDENCE
- If the serum TSH is subnormal, a radionuclide thyroid scan should be performed.

STRONG RECOMMENDATION
MODERATE-QUALITY EVIDENCE
- If the serum TSH is normal or elevated, a radionuclide scan should **not** be performed as the initial imaging evaluation.

STRONG RECOMMENDATION
MODERATE-QUALITY EVIDENCE

Serum thyroglobulin measurement

- Routine measurement of serum thyroglobulin (Tg) is **not** recommended.

STRONG RECOMMENDATION
MODERATE-QUALITY EVIDENCE

Haugen. ATA Nodule Guidelines Thyroid (in review) 2015.

How should a nodule identified incidentally by PET scan and confirmed by ultrasound be evaluated?

- Focal FDG-PET uptake within a sonographically confirmed thyroid nodule conveys an increased risk of thyroid cancer, and fine needle aspiration is recommended.

STRONG RECOMMENDATION
MODERATE-QUALITY EVIDENCE
- Diffuse FDG-PET uptake, in conjunction with sonographic and clinical evidence of chronic lymphocytic thyroiditis, does not require further imaging or fine needle aspiration.

STRONG RECOMMENDATION
MODERATE-QUALITY EVIDENCE

Haugen. ATA Nodule Guidelines Thyroid (in review) 2015.

Thyroid Nodule Sonographic Patterns and Malignancy Risk

Sonographic Pattern	US Features	Malignancy Risk	Consider Biopsy
High Suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with suspicious features	>70-90%	≥1 cm
Intermediate Suspicion	Hypoechoic solid nodule with smooth margins without suspicious features	10-20%	≥1 cm
Low Suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without suspicious features	5-10%	≥1.5 cm
Very Low Suspicion	Spongiform or partially cystic nodules without suspicious features	<3%	≥2 cm
Benign	Purely cystic nodules (no solid component)	<1%	No Biopsy

Suspicious Features
Irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension

Haugen. ATA Nodule Guidelines Thyroid (in review) 2015.

How are suspected hyperfunctioning nodules evaluated?

- Suspect an autonomous nodule if serum TSH is low or low-normal in patients with multiple nodules(s).
- A technetium 99 mTc pertechnetate or ¹²³I thyroid scan should be considered and directly compared to the ultrasound images to determine the functionality of each nodule >1 cm.
- FNA should then be considered only for isofunctioning or nonfunctioning nodules.

WEAK RECOMMENDATION LOW-QUALITY EVIDENCE

Haugen. ATA Nodule Guidelines Thyroid (in review) 2015.

How is ultrasound used to follow nodules with benign cytology?

- The follow up of thyroid nodules with **benign cytology** diagnoses is based upon the **ultrasound pattern**.
- **Nodules with high suspicion:** repeat US and US FNA
- **Nodules with low to intermediate suspicion:** repeat US at 12-24 months. If evidence of growth repeat
- **Nodules with very low suspicion:** If US is repeated, it should at >24 months

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

WEAK RECOMMENDATION LOW-QUALITY EVIDENCE

NO RECOMMENDATION INSUFFICIENT EVIDENCE

Haugen. ATA Nodule Guidelines Thyroid (in review) 2015.

Case 1 – Answers

48 year old male with incidentally found 2 x 2 cm thyroid nodule

- 1. Which tests should be obtained?**
A serum TSH should be measured. If normal to elevated, an ultrasound of the thyroid should be performed.
- 2. Should additional imaging be ordered?**
If serum TSH is suppressed, a radionuclide scan should be ordered.
- 3. Should the nodule undergo fine needle aspiration?**
Yes, all nodules >1-2 cm and confirmed by ultrasound in patients with a normal or elevated TSH should undergo FNA.
- 4. What is the risk of malignancy?**
Without other risk factors or suspicious ultrasound features, the malignancy risk is approximately 5-10%.

Hypothyroidism

Case 2

- A 42 year old man is seen to establish care at a new primary care center. He has been generally healthy, except for hypercholesterolemia treated with atorvastatin. He has noted some increased fatigue and a generally low energy level. He complains of a 5# weight gain and difficulty losing weight.
- **Family History**
 - Mother – Hypothyroid, Maternal Grandmother – Hypothyroid
- **Physical Examination**
 - P71, BP-132/83 Weight 187#, Height 68"
 - BMI 28.4
 - Neck-no thyroid enlargement detected
 - Chest and Cardiac-normal
 - Extremities-normal

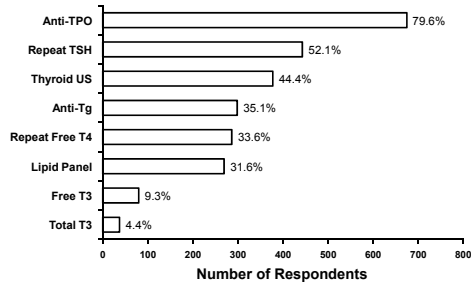
Case 2

TSH 7.45 mIU/L (nl .55-4.78)

Free T4 1.2 ng/dL (0.8-1.8)

1. Is the patient hypothyroid?
2. Are additional tests necessary?
3. Should he be treated with thyroxine?
4. If treatment is initiated, what dose should be started?
5. What are the potential benefits of treatment?

Initial Testing in Overt Hypothyroid Patient Based on Expert Survey



Burch, et al. *J Clin Endocrinol Metab.* 2014;99:2077.

Why is levothyroxine monotherapy considered to be the standard of care for hypothyroidism?

- Efficacy in resolving the symptoms of hypothyroidism
- Long-term experience of its benefits
- Favorable side effect profile
- Ease of administration
- Good intestinal absorption
- Long serum half-life (7-10 days)
- Low cost

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

Jonklaas J, et al. *Guidelines for the Treatment of Hypothyroidism Thyroid.* 2014; 24:1670.

Is there a clinical rationale for prescribing brand name levothyroxine preparations in preference to generic levothyroxine?

- Prescription of brand name levothyroxine, or maintenance of the same identifiable generic formulation of levothyroxine, is advised.
- Switches between levothyroxine products could potentially result in variations in the administered dose and should generally be avoided.

WEAK RECOMMENDATION LOW-QUALITY EVIDENCE FOR GENERAL POPULATION

Jonklaas J, et al. *Guidelines for the Treatment of Hypothyroidism Thyroid.* 2014; 24:1670.

What is the best approach to initiating and adjusting levothyroxine therapy?

- Thyroid hormone therapy should be initiated as an initial full replacement, or as partial replacement with gradual increments in the dose titrated upward using serum TSH as the goal.
- Dose adjustments should be made when there are large changes in body weight, with aging, and with pregnancy.
- TSH assessment 4-6 weeks after any dosage change.

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

Jonklaas J, et al. *Guidelines for the Treatment of Hypothyroidism Thyroid.* 2014; 24:1670.

What are the potential deleterious effects of excessive levothyroxine?

- The deleterious health effects of iatrogenic thyrotoxicosis include atrial fibrillation and osteoporosis.
- Avoid subnormal serum TSH values, particularly TSH values below 0.1 mIU/L, especially in older persons and postmenopausal women.

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

Jonklaas J, et al. *Guidelines for the Treatment of Hypothyroidism Thyroid.* 2014; 24:1670.

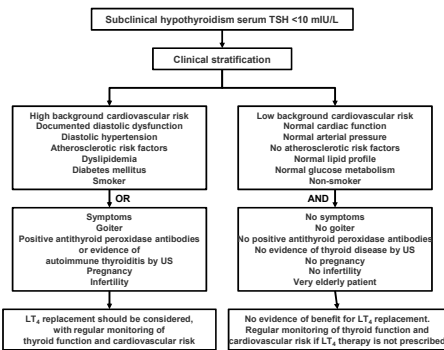
What factors determine the levothyroxine dose required by a hypothyroid patient for reaching the appropriate serum TSH goal?

- Patient's weight, lean body mass, pregnancy status, etiology of hypothyroidism, degree of TSH elevation, age, and general clinical context, including the presence of cardiac disease, should all be considered.
- The serum TSH goal appropriate for the clinical situation should also be considered.

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

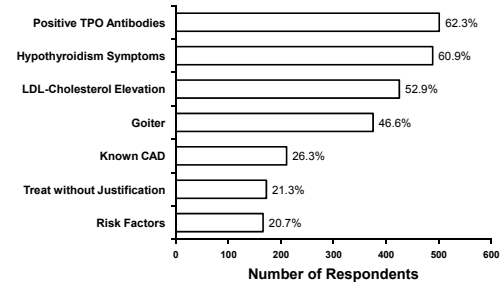
Jonklaas J, et al. *Guidelines for the Treatment of Hypothyroidism Thyroid.* 2014; 24:1670.

Evaluation of Subclinical Hypothyroidism



Biondi and Cooper. *Endocr Rev.* 2008;29:76.

Initiation of Thyroxine in a Patient with Subclinical Hypothyroidism



Burch, et al. *J Clin Endocrinol Metab.* 2014;99:2077.

Levothyroxine Formulations

% Increase	50	75	88	100	112	125	137	150	175	200
Dose (µg)	50	75	88	100	112	125	137	150	175	200
% Decrease	-33	-15	-12	-11	-10	-9	-9	-14	-13	

Difference of <25%

Difference ≤ 10%

Should levothyroxine therapy for hypothyroidism, particularly in specific sub-groups such as those with obesity, depression, dyslipidemia, or who are athyreotic, be targeted to achieve high-normal T3 levels or low-normal TSH levels?

- There is insufficient evidence of benefit to target low-normal TSH values or high-normal T3 values in those patients with hypothyroidism who are overweight, or those who have depression, dyslipidemia, or who are athyreotic.

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

Jonklaas J, et al. *Guidelines for the Treatment of Hypothyroidism Thyroid.* 2014; 24:1670.

*What biochemical goals should be employed for levothyroxine replacement in patients with **secondary** hypothyroidism?*

- The goal should be to maintain the serum free thyroxine values in the upper half of the reference range.
- The serum free thyroxine target level may be reduced in older patients or patients with comorbidities, who may be at higher risk of complications of thyroid hormone excess.

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

Jonklaas J, et al. *Guidelines for the Treatment of Hypothyroidism Thyroid.* 2014; 24:1670.

In adults requiring thyroid hormone replacement treatment for primary hypothyroidism who feel unwell while taking levothyroxine, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?

- There is currently insufficient evidence to support the **routine** use of a trial of a combination of levothyroxine and liothyronine therapy outside of a formal clinical trial, due to uncertainty in long-term risk benefit ratio of the treatment.

INSUFFICIENT EVIDENCE MODERATE-QUALITY EVIDENCE

Jonklaas J, et al. *Guidelines for the Treatment of Hypothyroidism Thyroid.* 2014; 24:1670.

What should be considered when patients on thyroxine alone have persistent symptoms?

Possible causes of persistent complaints in L-T4-treated hypothyroid patients:

- **Nonspecific causes:** related to the chronic nature of the disease
- **Specific causes:** related to thyroid disease and thyroid
 - Hormone replacement
 - Associated autoimmune diseases
 - Thyroid autoimmunity per se
 - Inadequacy of L-T4 dose
 - Inadequacy of L-T4 treatment modality

Wiersinga WM, et al. *ETA T4/T3 Guidelines Eur Thyroid J.* 2012;1:55-71.

How should levothyroxine administration be timed with respect to meals and beverages in order to maintain maximum, consistent absorption?

- Levothyroxine should be consistently taken either 60 minutes before breakfast or at bedtime (3 or more hours after the evening meal).
- Levothyroxine should be separated from other potentially interfering medications and supplements (e.g. calcium carbonate and ferrous sulfate). A 4-hour separation is traditional, but untested. Other medications (e.g. aluminum hydroxide and sucralfate) may have similar effects.

WEAK RECOMMENDATION MODERATE-QUALITY EVIDENCE

WEAK RECOMMENDATION WEAK-QUALITY EVIDENCE

Jonklaas J, et al. *Guidelines for the Treatment of Hypothyroidism Thyroid.* 2014; 24:1670.

Agents and Conditions Having an Impact on L-thyroxine Therapy and Interpretation of Thyroid Tests

Interference with Absorption:

- **Bile acid sequestrants** (cholestyramine, colestipol, colesevelam)
- **Sucralfate**
- **Cation exchange resins** (Kayexelate)
- **Oral bisphosphonates**
- **Proton pump inhibitors**
- **Raloxifene**
- **Multivitamins** (containing ferrous sulfate or calcium carbonate)
- **Ferrous sulfate**
- **Phosphate binders** (sevelamer, aluminum hydroxide)
- **Calcium salts** (carbonate, citrate, acetate)
- **Chromium picolinate**
- **Charcoal**
- **Orlistat**
- **Ciprofloxacin**
- **H2 receptor antagonists^a**
- **Malabsorption syndromes**
 - Celiac disease
 - Jejunioileal bypass surgery
 - Cirrhosis (biliary)
 - Achlorhydria
- **Diet**
 - Ingestion with a meal
 - Grapefruit juice^a
 - Espresso coffee
 - High fiber diet
 - Soybean formula (infants)
 - Soy

ATA/AACE Guidelines for Hypothyroidism. Garber JR, et al. *Thyroid.* 2012;22:1200-1235.

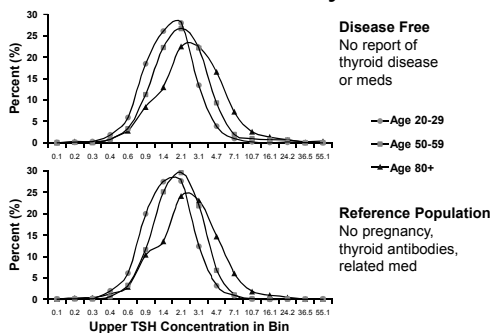
How should levothyroxine therapy be managed in the elderly with hypothyroidism?

- Levothyroxine should be initiated with low doses, and the dose titrated slowly based on serum TSH measurements.
- Normal serum TSH ranges are higher in older populations (such as those over 65 years), and higher serum TSH targets may be appropriate for those on thyroxine replacement.

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

Jonklaas J, et al. *Guidelines for the Treatment of Hypothyroidism Thyroid.* 2014; 24:1670.

Age Distribution of TSH from NHANES III Survey Data



Surks and Hollowell. *J Clin Endocrinol Metab.* 2007;92:4575.

Case 2 – Answers

42 year old male, hypercholesterolemia, TSH 7.45 mIU/L (nl .55-4.78), Free T4 1.2 ng/dL (0.8-1.8)

1. **Is the patient hypothyroid?**
The pattern of elevated TSH and normal range Free T4 is referred to as subclinical hypothyroidism.
2. **Are additional tests necessary?**
Most would measure a TPO antibody to confirm that it is autoimmune hypothyroidism and may progress to overt disease. This is strongly suggested by the family history, but it is not required to initiate treatment.
3. **Should he be treated with thyroxine?**
The patient has symptoms of fatigue and weight gain, as well as hypercholesterolemia.
4. **If treatment is initiated, what dose should be started?**
Most would begin full replacement as he is under 50 without evidence of CAD. A TSH measurement should be repeated in 4-6 weeks.
5. **What are the potential benefits of treatment?**
The patient may get some improvement in symptoms. Cardiovascular risk reduction with thyroxine treatment in the setting of subclinical hypothyroidism is most significant for middle-aged patients.

Hyperthyroidism

Case 3

- A 38 year old woman is seen with a 6 month history of excessive sweating, tremor, and a 10# weight loss.
- No family history of thyroid disease
- Medications-none

Physical Exam

- BP 124/74, P112, T 98.8, Weight 120#, 67#
- HEENT-bilateral lid lag, proptosis
- Neck-supple, thyroid gland 2-times normal size, diffuse, firm
- Ext-fine tremor of outstretched hands

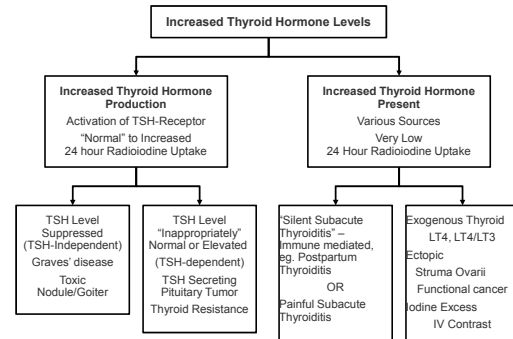
Case 3

Lab Results:

- TSH <0.05 (0.4-4.2 mIU/mL)
- FT4 3.2 (0.8-1.8 ng/dL)
- TT3 345 (80-200 ng/dL)

1. Should additional tests be performed?
2. What is the appropriate treatment?
3. How should the patient be monitored?
4. How long should treatment be continued?

Etiology of Increased Thyroid Hormone Levels



Causes of Thyrotoxicosis

Thyrotoxicosis associated with a normal or elevated radioiodine uptake over the neck^a

- Graves' Disease, Toxic Adenoma or Toxic Multinodular Goiter, Trophoblastic disease, TSH-producing pituitary adenomas, Resistance to thyroid hormone (T3 receptor mutation)^b

Thyrotoxicosis associated with a near-absent radioiodine uptake over the neck

- Painless (silent) thyroiditis, Amiodarone-induced thyroiditis, Subacute (granulomatous, de Quervain's) thyroiditis, Iatrogenic thyrotoxicosis, Factitious ingestion of thyroid hormone, Struma ovarii, Acute thyroiditis, Extensive metastases from follicular thyroid cancer

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

Bahn, et al. *Thyroid*. 2011;21:593.

When should a thyroid uptake and scan be performed in a patient with thyrotoxicosis?

- A radioactive iodine uptake should be performed when the clinical presentation of thyrotoxicosis is not diagnostic of Graves' Disease
- A thyroid scan should be added in the presence of thyroid nodularity.

STRONG RECOMMENDATION

LOW-QUALITY EVIDENCE

Bahn, et al. *Thyroid*. 2011;21:593.

Which patients with thyrotoxicosis should receive beta-adrenergic blockers?

- Beta-adrenergic blockade should be given to elderly patients with symptomatic thyrotoxicosis and to other thyrotoxic patients with resting heart rates in excess of 90 beats per minute or coexistent cardiovascular disease.

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

Bahn, et al. *Thyroid*. 2011;21:593.

Beta-Adrenergic Receptor Blockade

Drug	Dosage	Frequency	Considerations
Propranolol	10-40mg	TID-QID	<ul style="list-style-type: none"> • Nonselective beta-adrenergic receptor blockade • Longest experience • May block T4 to T3 conversion at high doses • Preferred agent for nursing mothers
Atenolol	25-100mg	QD or BID	<ul style="list-style-type: none"> • Relative beta1 selectivity • Increased compliance
Metoprolol	25-50mg	QID	<ul style="list-style-type: none"> • Nonselective beta-adrenergic receptor blockade, once daily • Least experience to date • May block T4 to T3 conversion at high doses
Esmolol	40-160mg	QD	<ul style="list-style-type: none"> • In intensive care unit setting of severe thyrotoxicosis or storm

Bahn, et al. *Thyroid*. 2011;21:593.

How should overt hyperthyroidism due to Graves' disease be managed?

- Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities:
- ¹³¹I therapy
- Antithyroid drugs (ATD)
- Thyroidectomy

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

Bahn, et al. *Thyroid*. 2011;21:593.

Which factors favor use of one of the three treatment modalities for Graves' hyperthyroidism?

Radioiodine ¹³¹I

- Females planning a pregnancy in the future (in more than 4-6 months following radioiodine therapy)
- Individuals with comorbidities increasing surgical risk
- Patients with previously operated or externally irradiated necks
- Lack of access to a high-volume thyroid surgeon
- Contraindications to antithyroid drug (ATD) use

Bahn, et al. *Thyroid*. 2011;21:593.

Which factors favor use of one of the three treatment modalities for Graves' hyperthyroidism?

Antithyroid Drugs (ATDs)

- High likelihood of remission (patients, especially females, with mild disease, small goiters, and negative or low-titer TSH-Receptor Antibody, TRAb)
- Elderly or others with comorbidities increasing surgical risk or with limited life expectancy...unable to follow radiation safety regulations
- Previously operated or irradiated necks
- Lack of access to a high volume thyroid surgeon
- Moderate to severe active Graves' Ophthalmopathy

Bahn, et al. *Thyroid*. 2011;21:593.

Which factors favor use of one of the three treatment modalities for Graves' hyperthyroidism?

Surgery

- Symptomatic compression or large goiters
- Low uptake of radioactive iodine
- Thyroid malignancy is documented or suspected or large nonfunctioning nodule
- Coexisting hyperparathyroidism requiring surgery
- Females planning a pregnancy in <4-6 months
- Patients with moderate to severe active Graves' Ophthalmopathy

Bahn, et al. *Thyroid*. 2011;21:593.

Which antithyroid drug should be used and how should treatment be initiated?

- Obtain baseline complete blood count, including white count with differential, and a liver profile.

WEAK RECOMMENDATION LOW-QUALITY EVIDENCE

- Methimazole should be used except during the first trimester of pregnancy, when propylthiouracil is preferred, in the treatment of thyroid storm, and in patients with minor reactions to methimazole who refuse radioactive iodine therapy or surgery.

STRONG RECOMMENDATION MODERATE-QUALITY EVIDENCE

- Patients should be informed of side effects of antithyroid drugs and the necessity of informing the physician promptly if they should develop.

WEAK RECOMMENDATION LOW-QUALITY EVIDENCE

Bahn, et al. *Thyroid*. 2011;21:593.

How long should Graves' disease patients be treated with antithyroid drugs and how should they be monitored?

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

WEAK RECOMMENDATION LOW-QUALITY EVIDENCE

- Methimazole should be continued for approximately 12-18 months, then tapered or discontinued if the TSH is normal.

STRONG RECOMMENDATION HIGH-QUALITY EVIDENCE

- If a patient with GD becomes hyperthyroid after completing a course of methimazole, consideration should be given to treatment with radioactive iodine or thyroidectomy.

WEAK RECOMMENDATION LOW-QUALITY EVIDENCE

Bahn, et al. *Thyroid*. 2011;21:593.

ATA/AACE Guidelines for Treatment of Subclinical Hyperthyroidism (suppressed TSH, normal T4/T3)

Factor	TSH (<0.1 mU/L)	TSH (0.1-0.5 mU/L)
Age >65	Yes	Consider treating
Age <65 with Comorbidities		
Heart Disease	Yes	Consider treating
Osteoporosis	Yes	No
Menopausal	Consider treating	Consider treating
Hyperthyroid Symptoms	Yes	Consider treating
Age <65, Asymptomatic	Consider treating	No

Bahn, et al. *Thyroid*. 2011;21:598.

Case 3 – Answers

38 year old woman with 6 month history of sweating, tremor and 10# weight loss, ophthalmopathy on exam. **Laboratory** – TSH <0.05 (0.4-4.2 mIU/mL), FT4 3.2 (0.8-1.8 ng/dL), TT3 345 (80-200 ng/dL).

1. Should additional tests be performed?

History, labs and the presence of ophthalmopathy are sufficient to diagnose Graves' disease. TSH receptor antibodies could be measured and a radionuclide uptake and scan performed, but these are not necessary.

2. What is the appropriate treatment?

Most would treat initially with beta blockers. Secondly antithyroid drugs may also be used. Radioiodine and surgery offered as alternative treatments.

3. How should the patient be monitored?

Baseline CBC and liver function tests should be measured. Patient should be cautioned regarding symptoms of agranulocytosis, such as fever or pharyngitis, and to stop antithyroid drug if they occur. Thyroid tests should be repeated in 1-2 months.

4. How long should treatment be continued?

Treatment is generally continued for 12-18 months to assess if a remission has occurred. This would be confirmed by a normal TSH off medication. Treatment, however, can be continued beyond this time if definitive treatment with radioiodine or surgery is refused or not possible.