Managing Thyroid Disease in General Practice: When to Hold 'Em and When to Fold 'Em…

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Disclosure

Consultant: Astra Zeneca; Bayer; Boehringer Ingelheim; Lilly; Merck; Novo Nordisk; Pfizer

Lectures: Astra Zeneca; Boehringer Ingelheim

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OBJECTIVES

1.) Identify, diagnose and treat virtually all patients with hypothyroidism

2.) Identify and diagnose patients with hyperthyroidism, and initiate therapy in selected cases and refer others to subspecialists.

3.) Understand the current evaluation of the thyroid nodule and refer as necessary those patients needing further evaluation or treatment to local specialists

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2. Hypothyroidism
3. Hyperthyroidism
4. Thyroid Nodules
5. Special Situations

When should the patient be managed in primary care (vs. referral to an endocrinologist)?

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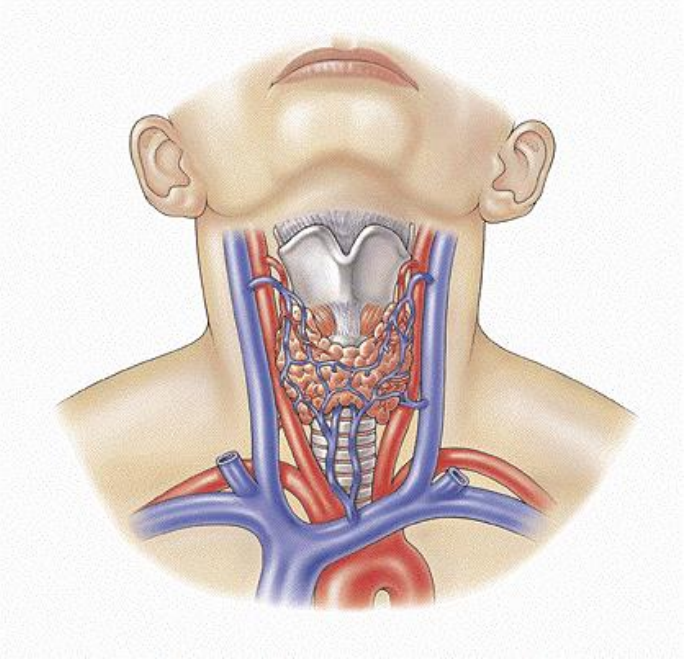

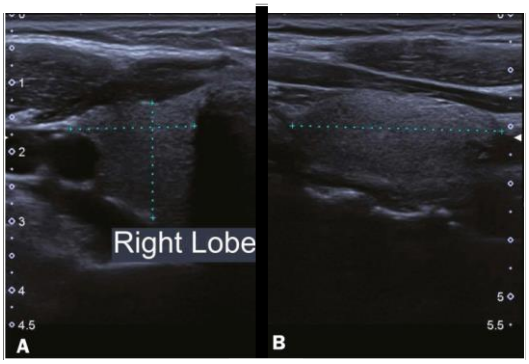

<u>Each lobe</u> (iodine replete)

- Height (rostro-caudal): 3-4 cm
- Width (medio-lateral): 1-2 cm
- Depth (antero-posterior): 2-3 cm
- Volume: 7-15 ml
- Weight: 10-20 g

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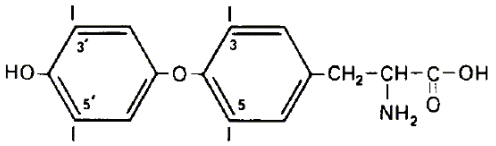
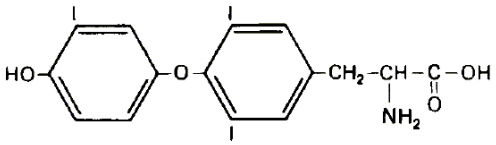
<u>Thyroid Hormones</u>

- Thyroid hormone released from the gland is mostly **T4** (about 100 mcg) and a small amount of **T3** (15%)
- Most of T3 (85%) is produced from T4 → T3 conversion in peripheral tissues by deiodinase enzymes
- T4 and T3 are 99% protein-bound in the serum (mostly to TBP*)
- Unbound or **'free' T4** and **'free' T3** are the <u>active</u> forms



3,5,3′,5′-Tetraiodothyronine (thyroxine, T_4)



3,5,3′-Triiodothyronine (T_3)

* Thyroid Binding Protein

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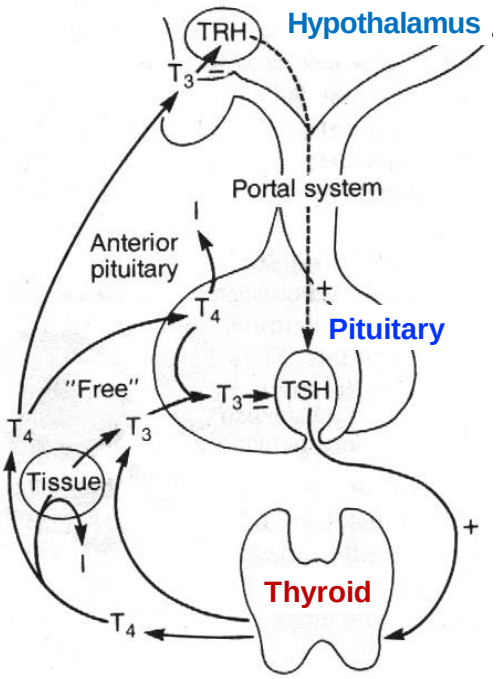
Control of Thyroid Hormone Secretion

RH → TSH → T4, T3

- Negative feedback from T3 on both TSH and TRH secretion
- A finely-tuned system!: Every 10% drop in FT4 results in a doubling of TSH secretion
- In most circumstances, the TSH level is the best arbiter of the patient's thyroid functional status



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The "Thyroid Toolbox"

LABS

- TSH
- Total T4
- Free T4
- Free Thyroxine Index (FTI)
- T3 Uptake (resin uptake)
- Total T3
- Free T3
- Thyroglobulin (TG)
- Anti-TPO Ab
- Anti-TG Ab

IMAGING

- Thyroid ultrasound
- Neck ultrasound (mapping)
- Thyroid nuclear scan (Tc99m)
- RAIU*
- Whole-body I-131 scan
- CT Neck
- MRI Neck
- PET scan

* Radioactive iodine uptake (I-123)

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The "Thyroid Toolbox"

LABS

- **TSH** ⟵ Best for screening (order as "Reflex to FT4")
- Total T4
- **Free T4** ⟵ Always include if you suspect thyroid disease (or in hospitalized patients)
- Free Thyroxine Index (FTI)
- T3 Uptake (resin uptake)
- **Total T3** ⟵ Only order if following hyperthyroidism
- Free T3
- Thyroglobulin (TG)
- **Anti-TPO Ab**
- Anti-TG Ab

IMAGING

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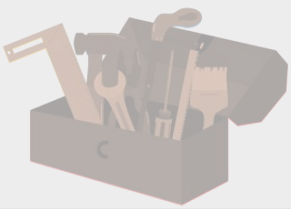

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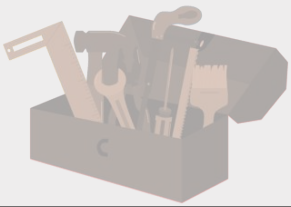
Order only when evaluating thyrotoxicosis, palpable nodules or goiter, or thyroid pain/tenderness →

Order only when evaluating thyrotoxicosis →



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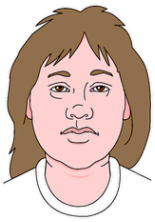
Signs/Symptoms of Hypothyroidism



SKIN/HAIR
- Cool, dry, pale (vasoconstriction)
- Yellowish palms (↑ carotene)
- Nonpitting edema (↑ hyaluronate)
- Myxedematous ('puffy')
- Periorbital edema
- Brittle hair / nails

CNS
- Cognitive dysfunction / dementia
- 'Myxedema madness'
- Slow movement / clumsy / ataxia
- Paresthesias/ carpal tunnel
- Delayed DTR relaxation phase

CV
- ↓ HR, ↓ contractility, ↓ CO
- ↑ PVR
- HTN with ↑ diastolic BP
- Pericardial effusion
- Cardiomyopathy

GI
- Modest weight gain
- ↓ appetite
- Constipation (↓ peristalsis)
- ↓ intestinal absorption
- ↓ Liver metabolism of meds
- Mild ↑ LFTs

RESP
- Pleural effusions
- Resp muscle weakness
- Hypoventilation / ↑ CO2

OTHER
- Fatigue, weakness
- Cold intolerance
- ↓ GFR
- Macrocytic anemia
- Menometrorrhagia

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Hypothyroidism / Myxedema

Kim J. *N Engl J Med* **2005**

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Causes of Hypothyroidism

Primary

- **Hashimoto disease (chronic lymphocytic thyroiditis)**
- **Recovery phase of thyroiditis** (viral, autoimmune)
- Post-thyroidectomy
- Anti-thyroid drugs (PTU, methimazole, carbimazole)
- Other meds (Li+, amiodarone, interferon- α, interleukin-2)
- Iodine deficiency; ingestion of dietary 'goitrogens'
- Enzymatic defects (iodification)
- Thyroid dysgenesis (agenesis or hypoplasia)
- Infiltrative diseases (sarcoid)

⇧ TSH
⇩ FT4

Secondary / Tertiary

- Hypopituitarism, hypothalamic dysfunction

⇩ TSH
⇩ FT4

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Work-Up of Primary Hypothyroidism

- H&P (symptoms, meds, FHx, thyroid exam, peripheral manifestations of hypothyroidism & other autoimmune conditions)
- Labs: TSH, FT4, (? Anti-TPO Abs)
- No imaging routinely needed. Get ultrasound only if a large goiter or if nodules are palpated.

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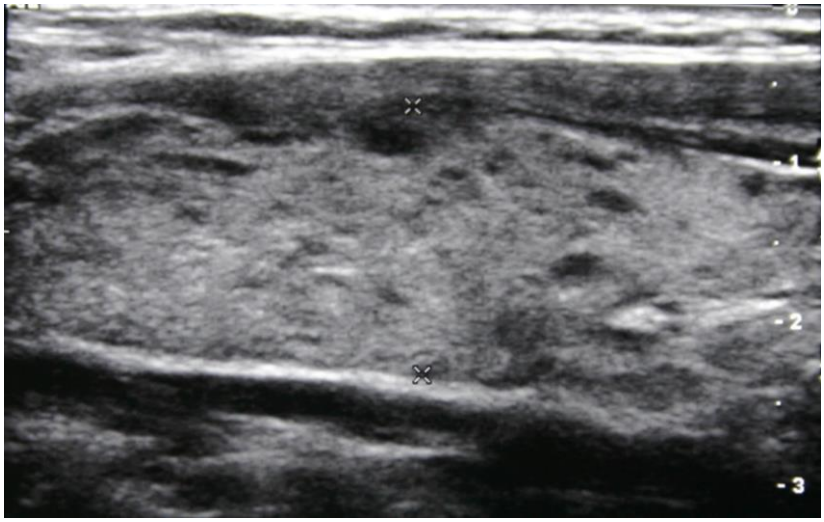
Ultrasound of Hashimoto's Disease



RIGHT SAG

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Treatment of Hypothyroidism

- Levothyroxine (LT4)* (synthetic T4) - 2 approaches…

  1. Full, athyreotic dose = 1.6 mcg/kg/day
     (Initially, reduce by 12-13 mcg to be conservative)
  2. Step-wise: start with 25-50 mcg and adjust to the TSH target
     (Best for older individuals and those with CAD, HF)

- TSH target: NL range, ideally 1-3 (sl. higher OK in elderly, lower in thyroid ca)
  - ↑ dose by 12-13 mcg if TSH<15-20; by 25 mcg if TSH >15-20
  - ↓ dose by 12-13 mcg if TSH ↓ but FT4 <10-20% above ULN; by 25 mcg if TSH ↓ and FT4 >20% above ULN (or if symptomatic)
  - ✓ TSH 6 wks after change (8 wks if TSH >50); once stable, Q 6-12 mo

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Treatment of Hypothyroidism

Levothyroxine (LT4)* (synthetic T4) - other points:

- Take on empty stomach, 30-60 min before food.
- Watch for drug-drug interactions (mostly ↓ absorption of LT4)
- Generics ≈ brand-name. However, remeasure TSH after 6 weeks if product brand changes.
- No clear benefit in most patients from natural thyroid (Armour thyroid)
- No clear benefit in most patients from liothyronine (Cytomel) or T3

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Things That Can Alter Thyroid Hormone Levels in Individuals Taking Levothyroxine

- Meds/supplements that bind LT4 (**iron**, **calcium**, aluminum-containing antacids, sucralfate, bile acid sequestrants, **soy**, high-fiber diets)
- Meds that affect gastric acidity (**PPIs**, H2 blockers)
- Meds that increase LT4 metabolism (**anti-seizure meds**)
- Meds that increase thyroid binding protein (estrogens, OCPs)
- Meds that can affect TSH secretion or T4 to T3 conversion (steroids, β-blockers)
- Meds that themselves can alter thyroid function (Li+, amio, iodinated contrast) – usually not an issue if there is zero thyroid hormone production.
- NOTE: If on **biotin**, hold for 3 days prior to TFT measurements (alters results from assays using biotin, e.g., falsely high FT4 and FT3 and falsely low TSH)

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Hypothyroidism: Special Circumstances

- Myxedema coma / severe hypothyroidism – needs IV LT4 (?ICU care)
- Treatment after thyroid cancer therapy
  - Lower TSH targets (<0.1-0.5 with normal FT4). Increase target during follow-up (0.5-2.0 if disease-free)
- Treatment during pregnancy
  - Increases of 25-50%+ are common (returns to baseline after delivery)
  - TSH target <2.0-2.5, FT4 in high-normal range (TFTs are moving targets in pregnancy)
  - More aggressive*, anticipatory dosing increases and more rapid TSH assessments are necessary
- Central hypothyroidism ('secondary') – do not check TSH, only FT4
- Alternative therapies ('natural' thyroid [Armour®], T3 [Cytomel®])
- If persistently high TSH: ?adherence vs. absorption
- 'Subclinical' hypothyroidism – who to treat?

*** ? Empiric increase by 2 pills per week**

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"Subclinical" Hypothyroidism

High TSH with normal free-T4

- More common in older women
- Progression to overt hypothyroidism = approx. 5%/year
- + anti-TPO Abs: progression to overt hypothyroidism more rapid/frequent
- Consider therapy if no contraindications and
  - ✓ symptomatic (!)
  - ✓ TSH >10 and/or progressing
  - ✓ goiter / nodules present
  - ✓ + anti-TPO Abs (?)
- Few data to suggest any important clinical advantages to earlier treatment

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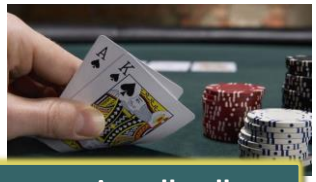

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2. Hypothyroidism
3. Hyperthyroidism
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5. Special Situation

- PCPs should be able to diagnose and manage virtually all forms of primary hypothyroidism.
- Referral of patients with persistent symptoms with normal labs only results in frustrated patients (and helpless endocrinologists!)
- If TSH not controlled, consider compliance, absorption issues, interfering meds. Refer only if your attempts at dose titration don't normalize TSH.
- Do refer for secondary hypothyroidism (i.e., pituitary disease), questions about treating subclinical disease, cases where the safety of therapy is a concern, or in women who are or are soon to become pregnant.

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Signs/Symptoms of Hyperthyroidism

SKIN/HAIR
- Warm, wet, flushed (vasodilated)
- Thinning hair
- Onycholysis
- Myxedema (Graves)
- Clubbing (Graves)

EYE
- Lid lag, lid retraction, stare
- Proptosis, ↓ vision (Graves)
- Diplopia (Graves)
- Periorbital edema (Graves)

RESP
- Dyspnea on exertion

CV
- ↑ HR, ↑ contractility, ↑ CO
- ↓ PVR
- HTN with ↑ systolic BP (↑ PP)
- Flow murmur
- Hyperdynamic precordium
- High-output HF

GI
- Weight loss w/ ↑ appetite
- Hyperdefecation (↑ peristalsis)
- ↓ intestinal absorption
- Mild ↑ LFTs
- ↑ Liver metabolism of meds

CNS
- Nervousness, anxiety
- Emotional lability
- Inability to concentrate
- Tremor
- Hyper-reflexia

OTHER
- Fatigue, weakness
- Oligomenorrhea

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Physical Exam Findings in Graves Disease








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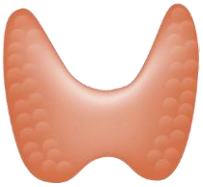
Causes of Hyperthyroidism*

*thyrotoxicosis

TSH-independent (Primary)

- **Graves disease**
- **Thyroiditis** (silent/postpartum, subacute, meds
- **Toxic multinodular goiter**
  - Iodine-induced (Jod-Basedow effect)
- **Toxic nodule** (single adenoma)
- Hydatidiform moles and choriocarcinomas
- Struma ovarii
- Iatrogenic / factitious



⇩ TSH
⇧ FT4

TSH-dependent (Secondary)

- TSH-secreting pituitary adenoma
- Selective pituitary resistance to thyroid hormone

⇧ TSH
⇧ FT4

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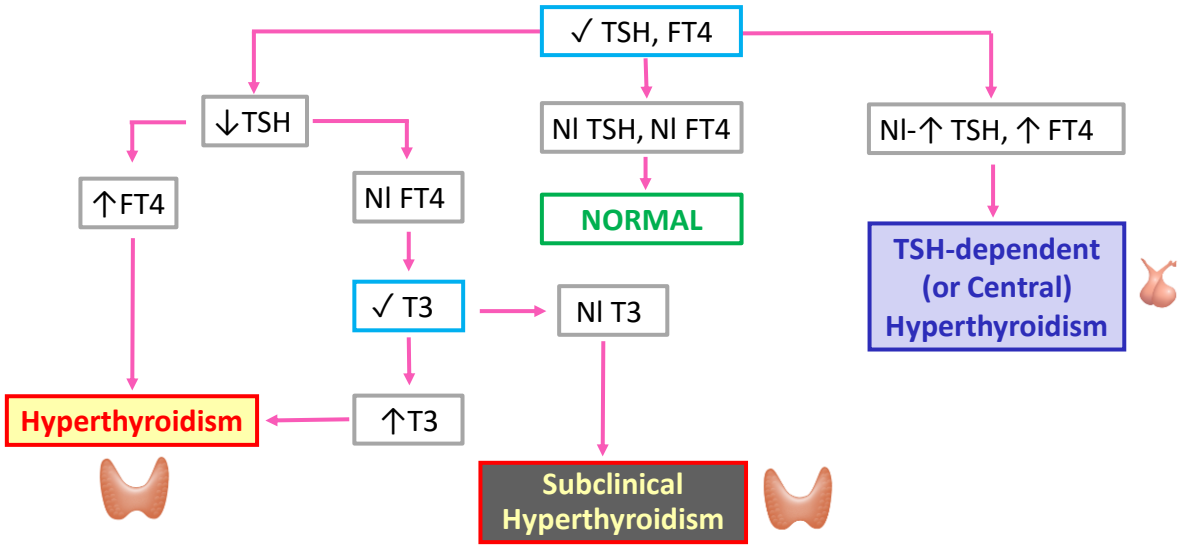
Laboratory Evaluation in Patients with Suspected Hyperthyroidism



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Differentiating the Cause of Thyrotoxicosis

- History (longer duration → Graves vs. thyroiditis)
- Physical (goiter, exophthalmos, pretibial myxedema, clubbing → Graves)
- Thyroid Stimulating Immunoglobulin (TSI)
- *or* TSH Receptor Antibody (TRAb)

(+ → Graves)

- Total T3 : Total T4 Ratio (>20 → Graves)
- Ultrasound (enlarged gland, heterogeneity, hyperemia → Graves)
- I-123 Radioactive Iodine Uptake (RAIU)
- Thyroid scan (Technetium 99m)

(↑RAIU, diffuse uptake→ Graves)

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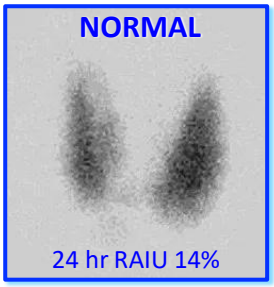
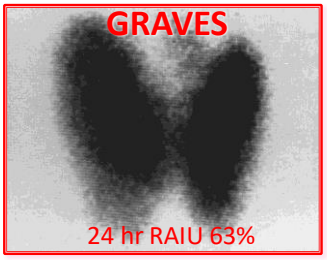
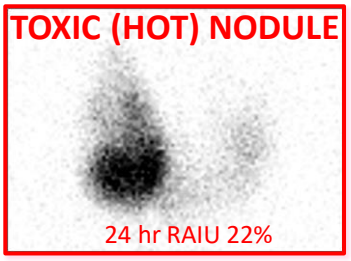
Thyrotoxicosis & Thyroid Scans*: What's the Diagnosis?







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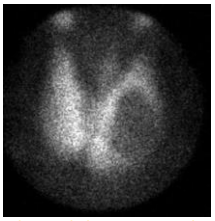
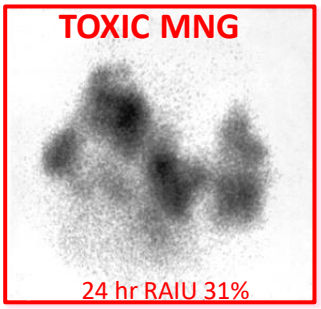
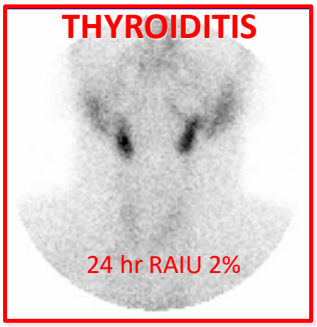


*Radionuclide scintigraphy w/ Tc-99m pertechnetate





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3 Treatment Options for Hyperthyroidism

1. **Anti-thyroid medications** (thionamides), often long-term
   - Methimazole (MMI): Start 10-60 mg/day given QD-BID, 2.5-20 mg/day given QD-QOD for maintenance
   - Propylthiouracil (PTU): Start 200-1200 mg/day given BID-TID, 100-300 mg/day QD-BID for maintenance

Instruct about possible side effects, especially rashes, hepatitis, & agranulocytosis

➢ Beta-blockade (for tachycardia, palpitations, anxiety, tremor only)

2. **Radioactive iodine** (RAI) (I-131, lower doses than used in thyroid ca)

- goal is to induce permanent hypothyroidism with LT4 replacement
- consider PTU/MMI pretreatment if very toxic
- can exacerbate thyroid eye disease (especially in smokers)

3. **Surgery** (near-total thyroidectomy)
   - PTU/MMI pre-treatment; SSKI or Lugol's solution (iodine) pre-operatively

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Side Effects of Antithyroid Drugs

- Common

Rashes, Urticaria	5-10%
Arthralgias	5%
Transaminitis (PTU > MMI)	5%

- Uncommon

Severe hepatitis (PTU > MMI)	1/1000
Agranulocytosis	2 - 3/1000
Cholestasis (MMI)	rare
Vasculitis	rare
Fetopathy (aplasia cutis, other) (MMI)	rare

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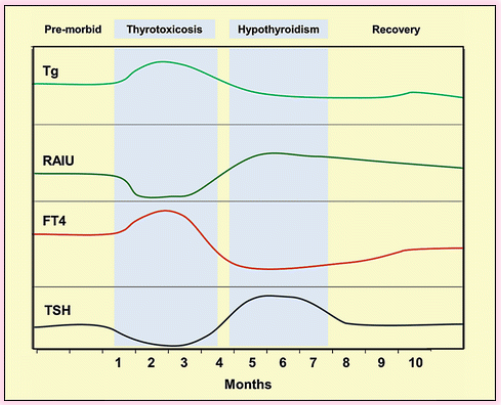
Unique Features of Thyroiditis

- Younger patients
- No goiter or mild enlargement; no extrathyroidal signs of Graves disease
- ↑ ESR; TPO Abs may be **+** (but TSI and TRAb usually –)
- Various types:
  - Acute, purulent (bacterial)
  - Lymphocytic / Silent / Post-partum
  - Granulomatous / Subacute / Painful
  - Drug inducted (amiodarone)
  - Traumatic
- Hyper → Hypo → Euthyroid
- Treat with β-blockers, NSAIDs / steroids



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"Subclinical" Hyperthyroidism

Low TSH with normal free-T4

- ↓ TSH, Normal FT4 and FT3
- Etiology could be Graves, toxic MNG or solitary toxic nodule
- Progression to overt hyperthyroidism low:
  - 1-2% per year (women > men)Men 0% per year
  - Toxic MNG may progress more frequently (5%/year)
- Indications to Rx:
  - Any cardiac disease (CAD, Afib, etc.)
  - Age > 60 (Relative Risk for Afib = 3x)
  - Osteoporosis

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- If you have ready access to an endocrinologist, it is customary to refer all those with thyrotoxicosis.
- However, there is no reason PCPs cannot diagnose and medically manage most cases, particularly thyroiditis (which is self limited) or mild Graves (which responds well to low-dose anti-thyroid drugs.)
- Consider endocrine referral if the patient desires surgery or RAI or if inadequate response to initial therapy.
- Refer if thyrotoxicosis during pregnancy or if severe sequelae of disease (hospitalization, thyroid storm, etc.)

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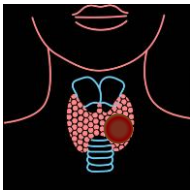
Thyroid Nodules



- Prevalence
  - Palpable: 4-7%
  - Non-palpable (by US): Age – 20% = ___% with nodules
- Usual size 1 – 3 cm
- Women > Men
- Typically asymptomatic and incidentally discovered (carotid US, chest CT)
- Thyroid function usually normal
- < 1% hyperthyroid
- < 5% cancerous (most common, indolent papillary carcinoma [70-80%])

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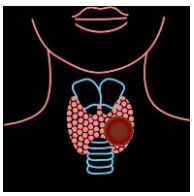
Thyroid Nodules: Causes



Benign (95%)

- Simple cyst
- Colloid nodule
- Hyperplastic nodule (Multinodular goiter)
- Follicular adenoma
- Hashiomoto thyroiditis

Malignant (5%)

Papillary carcinoma 70-80%
- Follicular variant
- Insular carcinoma
- Tall cell variant

Follicular carcinoma 15%
- Hürthle cell variant

Medullary carcinoma <5%

Lymphoma <5%

Anaplastic carcinoma <1%

Metastases <1%

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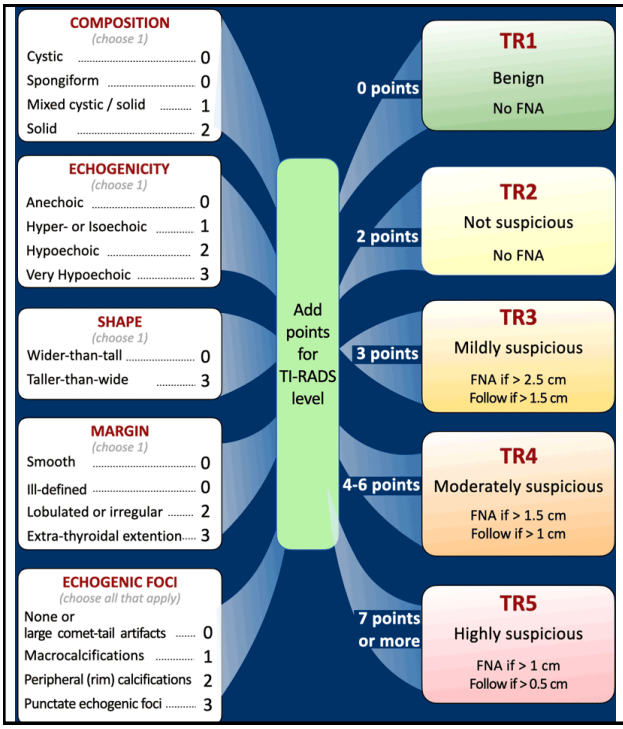

American College of Radiology's Thyroid Imaging, Reporting & Data System (TI-RADS):

- The 5 ultrasound features of thyroid nodules used in TI-RADS are: composition, echogenicity, shape, margin and punctate echogenic foci. Each item is given points.
- The points are added from all categories to determine the TI-RADS level, each with a recommendation.
- Nodules smaller than 5 mm do not need any follow-up, even if they are TI-RADS 5. This is because it is very unlikely that nodules smaller than 5 mm will become a clinical significant malignancy.
- The cutoff point of 2.5 cm for fine needle aspiration (FNA) in mildly suspicious TR3 lesions is based on studies showing that thyroid carcinomas don't have a decreased survival until they reach this threshold value.
- The ACR-TIRADS category has been shown to have good correlation with the malignancy risk in large studies. The risk of malignancy is:
  - **TR1: 0.3%**
  - **TR2: 1.5%**
  - **TR3: 4.8%**
  - **TR4: 9.1%**
  - **TR5: 35%**

Tessler FN *et al. J Am Coll Radiol* 2017;14:587-595;
https://radiologyassistant.nl/head-neck/ti-rads/ti-rads

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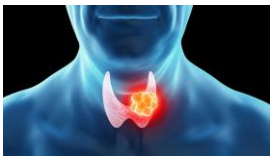
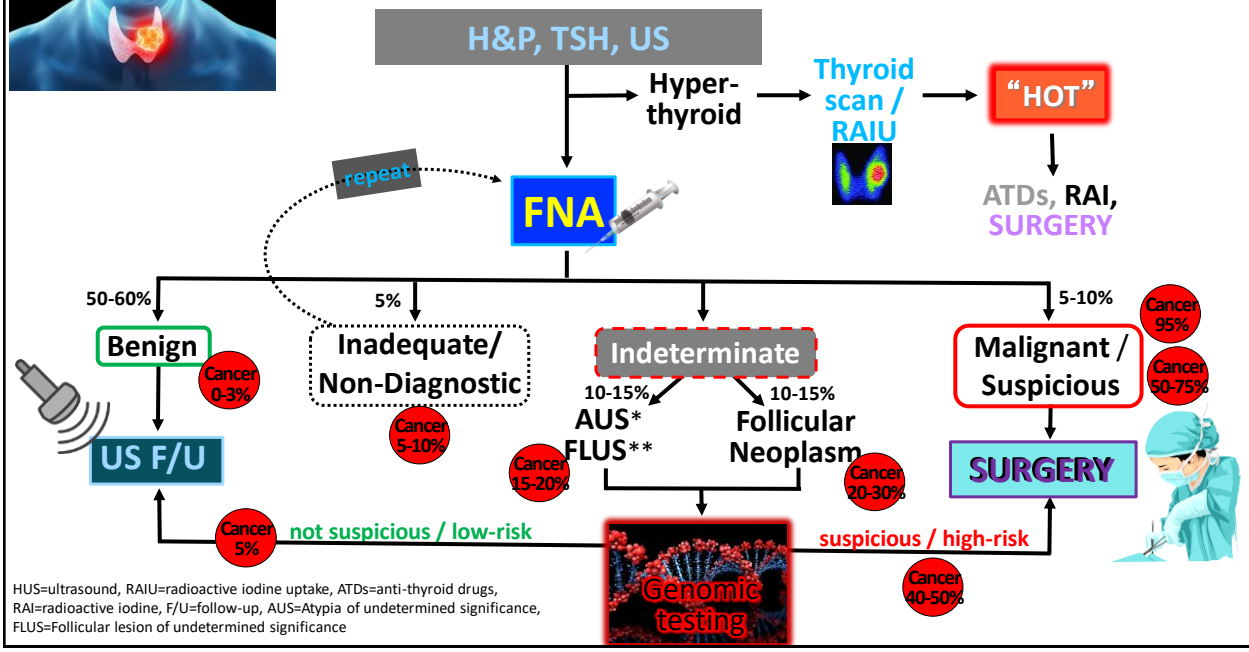


Thyroid Nodule Algorithm



HUS=ultrasound, RAIU=radioactive iodine uptake, ATDs=anti-thyroid drugs, RAI=radioactive iodine, F/U=follow-up, AUS=Atypia of undetermined significance, FLUS=Follicular lesion of undetermined significance

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Managing Thyroid Disease in General Practice: When to Hold 'Em and When to Fold 'Em . . .

1. Thyroid Anatomy & P
2. Hypothyroidism
3. Hyperthyroidism
4. Thyroid Nodules
5. Special Situations

- Work-up of thyroid nodules could be initiated by PCPs, starting with TFTs and US.
- The ACR TI-RADS grading system easily identifies which nodule(s) need biopsy and which need just follow-up. (The grade should be found within the report.)
- Consider ordering US-guided FNAs of the largest/most suspicious nodule (1 or at most 2) and then refer all but benign results.
- If you prefer to defer the evaluation to endocrinology (or endocrine/ENT surgery), these preliminary tests will still speed up the diagnostic process.

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Managing Thyroid Disease in General Practice: When to Hold 'Em and When to Fold 'Em . . .

1. Thyroid Anatomy & Physiology Pri
2. Hypothyroidism
3. Hyperthyroidism
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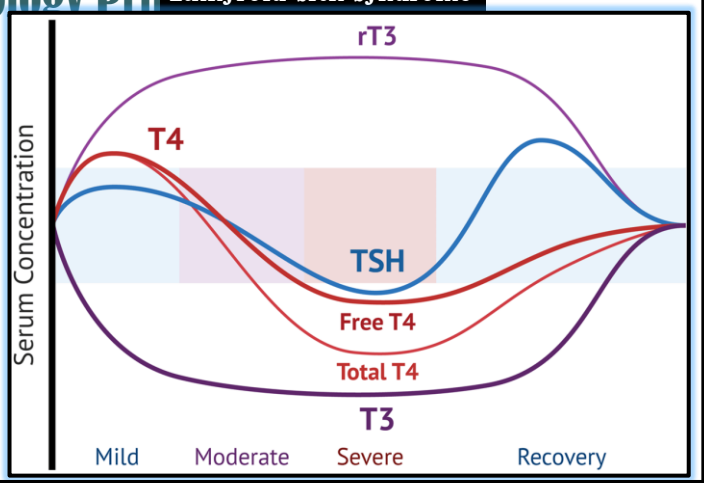
5. Special Situations

Euthyroid-Sick Syndrome



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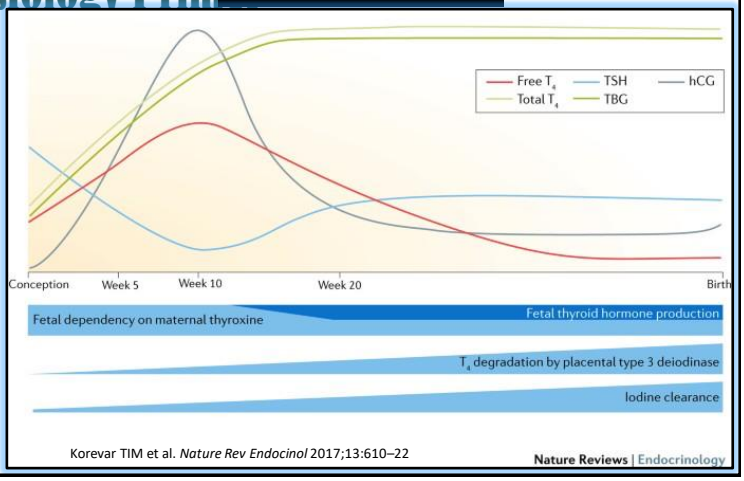
Managing Thyroid Disease in General Practice: When to Hold 'Em and When to Fold 'Em . . .

1. Thyroid Anatomy & Physiology Prim
2. Hypothyroidism
3. Hyperthyroidism
4. Thyroid Nodules
5. Special Situations

Thyroid in Pregnancy



Korevar TIM et al. *Nature Rev Endocinol* 2017;13:610–22

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