Thyroid Physiology, Pharmacology, & Pharmacotherapy

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Thyrotoxicosis / "Thyroid Storm" Therapy

Below adapted from S Med J 2002;95:493-505, Endocrinol Metab Clin N Am 2006;35:663-686, Chiha M, J Intensive Care Med 2015;30:131–40, ATA-AACE Guidelines. Thyroid 2016; 26: 1343–421.

DIAGNOSIS: Burch/Wartofsky score: 45+ pts=storm. <25 pts=no storm. 26-44 pts=impending storm. [Endocrinol Metab Clin North Am 1993;22:263–277.]

MANAGEMENT:

1. Control acute symptoms: Propranolol 10-80mg PO/NG q4-6h or 1-2mg slow IV push q15mins, OR Metoprolol 25-50mg PO q8-12h, OR Nadolol 40-160mg PO q24h, OR Atenolol 25-100mg q12-24h, OR Esmolol 0.25-0.50mg/kg load + 0.05-0.1mg/kg/min infusion. Target: HR<100 bpm.
2. Inhibit further T4 production: PTU 500-1000mg PO/NG load + 250mg q4h OR MMI 60-80mg PO daily.
3. Hydrocortisone 300mg IV load + 100mg IV q8h OR dexamethasone 0.5-2mg PO/NG q6h (blocks T4->T3 and may inhibit T4 release, prevents relative adrenal insufficiency)
4. Vigorous correction of fluid deficits and electrolyte imbalances.
5. Hyperthermia management with acetaminophen & cooling blankets.
6. Treatment of infection, other precipitating causes.

Questionable/possible therapies:

Prevent release of existing T4 with K-iodide 130mg cap PO/NG/PR 1 hour after thionamide (giving I- before thionamide could cause further T4 production/release); OR 15 drops of saturated solution of potassium iodide (SSKI), then 5 drops PO q6h; OR 1mL (4-8 drops) Lugol's solution (KI, N/A in Canada) PO TID. Use x 3-7 days or until resolution.

Types of Hyperthyroidism & Management: [ATA-AACE Guidelines. Thyroid 2016; 26: 1343–421]

B-blockers (e.g., atenolol 25-200mg QD) useful for symptom reduction (palpitations, tachycardia, tremulousness, anxiety, heat intolerance) regardless of cause/type.

High I131 uptake (oversynthesis):

Graves' Disease: thyroid-stimulating immunoglobulins which act like TSH (TRAb). Accompanied by goiter + orbitopathy (proptosis). Most common cause of hyperthyroidism. Therapy: (1) RAI (2) Subtotal thyroidectomy (3) Thionamides (see box). All 3 options equal biochemical outcomes at 6 weeks and 2y satisfaction & sick leave outcomes. Most relapse with thionamides, more orbitopathy with RAI. None help orbitopathy. (J Clin Endocrinol Metab 1996;81:2986-93)

Hashitoxicosis: Early stages of Hashimoto's thyroiditis may exhibit hyperthyroidism (later hypothyroidism). Therapy: Hyperthyroidism is transient, so use B-blockers. ASA/steroids only if tender.

Toxic Adenoma + Multinodular goiter: TSH-independent thyroid adenomas due to TSH receptor mutations. Therapy: RAI. Surgery is less preferable.

Iodine-induced: rare. Therapy: decrease iodine intake. Radioiodine if underlying adenoma.

Trophoblastic diseases: hydatiform mole or choriocarcinoma and Germ cell tumors: testicular. Therapy: Thionamides + surgery.

TSH-mediated: rare. Pituitary adenoma. Therapy: Surgery, octreotide 50-750mcg SC bid-tid supresses TSH, dopamine agonists (bromocriptine 10-20mg/d, cabergoline 0.25-0.5mg 1-2x/wk).

Low (<1%) I131 uptake (thyroiditis, overstimulation, extrathyroid source):

Thyroiditis: post-viral (de Quervain's, granulomatous, giant-cell, creeping), lymphocytic/silent/painless, postpartum, amiodarone-induced, radiation, interferon alpha-induced, palpation (parathyroid surgery)-induced. Therapy: NSAIDs, B-blockers, steroids (if painful), iopanoic acid (see box). Thionamides useless.

Exogenous/Ectopic: overdose (use B-blocker), "Struma ovarii" (surgery), follicular thyroid cancer metastases (surgery).

Subclinical Hyperthyroidism [ATA 2016 Guidelines. Thyroid 2016;1343-1421]

Definition: TSH <0.1 + Normal fT4.

~~1% prevalence in community, 14-21% in L-thyroxine-treated patients

Issues: Increased total (HR 1.24) & CHD mortality (HR 1.29), sudden cardiac death [Circulation 2016;6SEP], atrial fibrillation (HR 1.7) [Arch Intern Med. 2012;172(10):799-809], fractures (HR 1.38 hip, 1.20 non-spine) [Ann Intern Med 2014;161:189-99], possibly more risk in men [Arch Intern Med 2010;170:1876-83], progression to hyperthyroidism.

Management: in absence of underlying hyperthyroid diagnosis (e.g., Graves'), no evidence that treatment alters any of these outcomes. HOWEVER, ATA 2016 recommends treating all people >65, pts with CV risk factors, CV disease, osteoporosis, postmenopausal women not on estrogen or bisphosphonate, anyone with symptoms. Treatment is the same as overt hyperthyroidism. If not treating, regular thyroid monitoring in all patients to detect overt hyperthyroidism.

Management of amiodarone-induced hyperthyroidism (3%)

J Clin Endocrinol Metab, June 2010, 95(6):2529 –2535

Type I (increased T3 & T4 synthesis) "Jod Basedow"

-mainly in I-deficient areas & in patients with underlying multinodular goitre

-treat with thionamides (MMI 40-60 mg/d)+K-perchlorate (KClO4) 0.5-1g/d for first 2-6 weeks. Several weeks required to achieve euthyroidism. If refractory: thyroidectomy.

-may continue amiodarone

-response slow regardless of discontinuation of amiodarone d/t its long t1/2

Type II (thyroiditis) - most common form

-treat with corticosteroids. Thionamides not usually helpful.

-usually discontinue amiodarone

NOTE: Usually difficult to distinguish between Type I & II.

Radioiodine (I-131, RAI) in Graves' Disease

-given PO as solution or capsule

-Goal: high dose [10–15 mCi (370–555 MBq)] to render the patient with GD hypothyroid

-may cure or worsen proptosis in Graves' (give prednisone 20-40 mg/d x 2-3 months starting 5-7 days after RAI in patients with severe ophthalmopathy - NEJM 1998;338:73-8)

STRATEGY: Use MMI before and after giving RAI in pts at risk of severe consequences of thyrotoxicosis (which is rare): e.g. patients with HF AF, stroke, pulmonary HTN, CRF, COPD, poor diabetes control. Stop MMI 2-3 days before dose to prevent failure. Consider restarting MMI 3-7 days after RAI if at risk for severe hyperthyroid Sx. Thionamides reduce the success rate if given in the week before or after RAI treatment [BMJ. 2007; 334: 514]. Start B-blocker before RAI to prevent acute S&Sx. Radiation thyroiditis (1%): treat with NSAIDs. Avoid sharing cups or utensils, sexual contact, close contact with children and pregnant women x 1 week.

MONITORING: **Measure TSH, fT4, T3 1–2 months after RAI, then q4-6 weeks x 6 mos, or until hypothyroid and stable on T4 replacement.** 20% require second dose 6-12 months after initial dose. 40% of patients are hypothyroid @ 8 weeks and >80% by 16 weeks. Delay pregnancy for 6-12 months after therapy. Re-Treat with RAI if still hyperthyroid @ 6mos.

Thionamides (ATDs): methimizole (MMI) & propylthiouracil (PTU) in Graves' disease

Used to attain euthyroid state, either before/after RAI or thryroidectomy or for chronic GD therapy. 20-30% have prolonged remission after 1-2y of thionamide therapy.

MMI: Almost always preferred. More rapid onset (~80% euthyroid @ 10 weeks, 5.8 weeks to normalization vs. ~50% with PTU, 16.8 weeks to normalization - J Clin Endocrinol Metab 1987;65:719-23), once-daily dosing (vs. q8h with PTU), fewer serious adverse effects. 10 or 15mg PO once daily (similar response as 30 or 40mg/d) (Clin Endocrinol 1995;43:257-63, J Clin Endocrinol Metab 2007;92: 2157-62). Initial dose to achieve euthyroidism: 10-20mg daily, sometimes 30mg daily if severe sx. Once euthyroid taper to lowest effective maintenance dose (5-10mg daily) based on labs. Teratogenic – use PTU instead in 1st trimester of pregnancy. KI 38mg/daily + MMI 15mg daily produced better hyperthyroidism control and fewer ADRs than MMI 30mg alone (Thryoid 2015;25:43-50).

PTU: Preferred in 1st trimester of pregnancy, less severe birth defects than MMI. 100mg PO tid or 150 tid if large goitre or severe hyperthyroidism. Relevance of inhibition of peripheral T4->T3 conversion questionable. Single-daily-dose trials (150mg QD) show inferior efficacy to MMI 15mg QD (Clin Endocrinol.2004;60:676-81, 2001;54:385-90.)

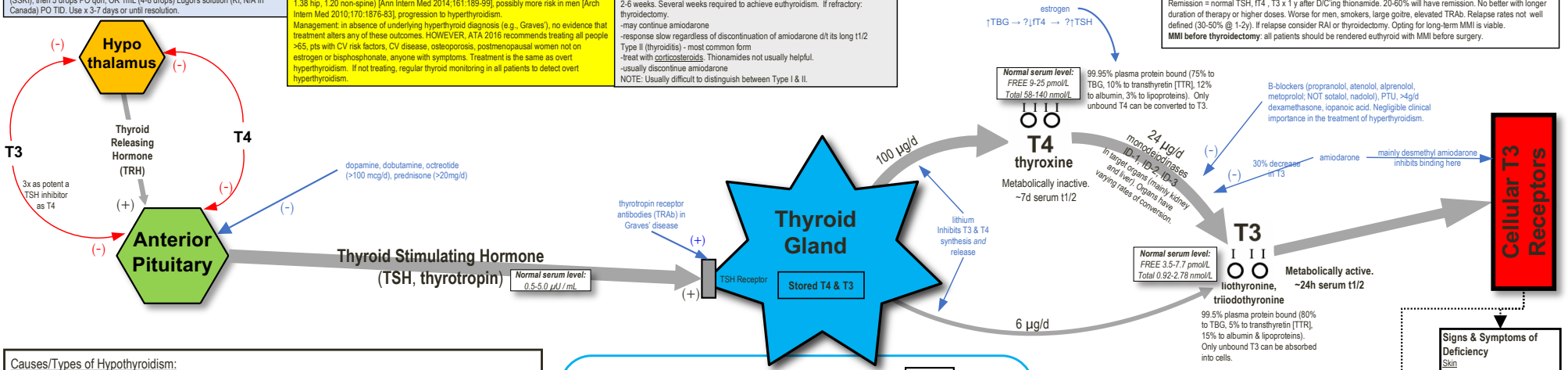
Toxicity: Common (~13%): pruritus, rash, urticaria, arthralgias, arthritis, fever, abnormal taste sensation, nausea/vomiting. 33% have transient liver enzyme elevation with PTU. Excessive initial doses cause hypothyroidism. Rare/Serious: agranulocytosis (0.2-0.5%, rapid recovery on discontinuation) Dose-dependent with MMI [4%vs.0.3% over 10 years with 30mg vs. 15 mg/d (Endo J 2007;54:39-43)]. Cholestatis with MMI. Liver failure (sometimes fatal) with PTU. Up to 38% ANCA positivity with PTU (vs. 0% with MMI) but vasculitis is rare.

Goal: Euthyroidism within 4-8 weeks.

Monitoring: CBC & LFTs at baseline before starting. q4-6 weekly TSH, fT4, T3 (TSH may take several months to recover). After TSH normalizes, no need to continue fT4/T3 monitoring. Most do not recommend routine CBCs or LFTs, but advise pts to seek attention at first sign of fever or pharyngitis, abdominal pain, dark urine, change in stools.

Duration: Treat for 12-18 mos, then if low/zero TRAb and normal TSH, taper/withdraw to assess for remission. Remission = normal TSH, fT4 , T3 x 1 y after D/C'ing thionamide. 20-60% will have remission. No better with longer duration of therapy or higher doses. Worse for men, smokers, large goitre, elevated TRAb. Relapse rates not well defined (30-50% @ 1-2y). If relapse consider RAI or thyroidectomy. Opting for long-term MMI is viable.

MMI before thyroidectomy: all patients should be rendered euthyroid with MMI before surgery.



Causes/Types of Hypothyroidism:

PRIMARY [Subclinical (TSH >4.5, fT4 Normal) or Overt (TSH>10, fT4 low)]

Chronic autoimmune/lymphocytic (Hashimoto's) thyroiditis: most common cause of hypothyroidism. Mainly older women. Anti-TPO (thyroid peroxidase) antibodies present in 75% of cases.

Iatrogenic: radioiodine, external Neck radiation, thyroidectomy

Iodine: deficiency (urine iodone <45 mcg/d) or excess

Drugs: rifampin, carbamazepine, phenobarbital, phenytoin, valproate, estrogen (NEJM 2001;344:1743-9), cholestyramine, sucralfate, FeSO4, AlOH, CaCO3, lithium, interferon alpha, sunitinib, PPI?, coffee?. Numerous mechanisms. More drugs (amiodarone, steroids, Bblockers) are depicted on this page.

Infiltrative diseases: hemochromatosis, scleroderma, leukemia, tuberculosis.

SECONDARY: TSH deficiency (<1% of hypothyroid cases): Pituitary necrosis (eg. Sheehan's syndrome), trauma, pituitary tumors. Treat with Thyrotropin (TSH, Thyrogen). Usually also need to replace other pituitary hormones.

TERTIARY (Central): TRH deficiency (<1% of hypothyroid cases): Hypothalamic damage from tumors, trauma, radiation therapy, or infiltrative diseases. Treat with Protirelin (TRH, Relefact TRH). Usually also need to replace other pituitary hormones.

Management of Primary Hypothyroidism [AACE/ATA Guidelines 2012; Endocr Pract 2012;18:989-1027.]

Goal: Normalize TSH, T4, T3 + eliminate S&Sx.

THERAPEUTICS:

Synthetic Levothyroxine (T4): Young healthy adults: Start "full replacement dose": 1.6 mcg/kg/d. ELDERLY: Start 50 mcg/d. CAD: Start 12.5-25 μg/d and monitor for angina. 12.5-25 mcg/d dosage adjustments. Initiate with T4 monotherapy. T4+T3 not superior to T4 alone on body weight, lipids, symptoms, cognition, QOL. IV formulation available (500μg/vial = $125). Mean dose required 1.6 μg/kg (50-200 μg/d); may be 1 μg/kg/d in elderly (50-100 μg/d).

MONITORING: Re-measure TSH 4-8 weeks after initiation or dose change. Questionable role for fT4, no role for T3 in routine monitoring. TSH annually once stable & when conditions change. Avoid chronically low TSH even if asymptomatic due to osteoporosis risk (TSH <0.1 → 3.6 x ↑ in hip fracture risk & 4.5 x ↑ in vertebral fracture risk vs. normal TSH in women >65 y/o. [Ann Intern Med 2001;134:561-568, BMJ 2011;342:d2238].

NOTES: Targeting lower half of TSH range no better than upper half w.r.t. Sx, QOL, cognition. [JCEM 2006:91: 2624 –2630]. Factors possibly requiring UPWARD dosage adjustment: worsened thyroid function, pregnancy, hi-fiber diet, concurrent rifampin, carbamazepine, phenobarbital, phenytoin, estrogen (NEJM 2001;344:1743-9), cholestyramine, sucralfate, FeSO4, AlOH, CaCO3 (JAMA 2000;283:2822), lithium, nephrotic syndrome [Eur Thyroid J 2015;4(2):138-142]. ASSESS ADHERENCE (most common reason).Factors possibly requiring DOWNWARD dosage adjustment: nephrotic syndrome, weight loss, androgen therapy.

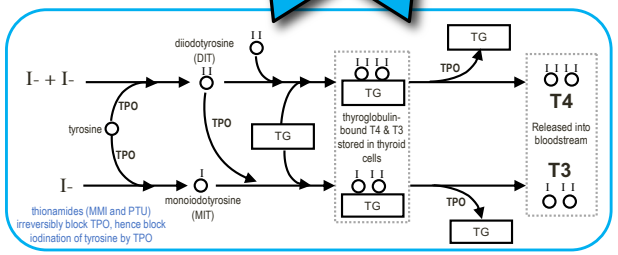
Primary Hypothyroidism & Pregnancy [ATA Guideline 2017; Thyroid 2017;27:315-389]

Screening in normal healthy women: no consensus. Recommendations range from screen all women before pregnancy (AACE) to screen only if high-risk (family history or goiter) (ATA, ACOG). TREAT with T4 if TSH > ~4 mU/L.

If not on T4 therapy prior to pregnancy, no consensus about optimal initial dose. Some suggest 1.2-1.4 mcg/kg/d initially [Thyroid. 2013;23(11): 1479-1483]. A retrospective study showed T4 50mcg/d (avg) was associated with reduced pregnancy loss and increased preterm delivery, preeclampsia, gestational diabetes. [BMJ 2017;356:i6865]

Women with pre-existing primary hypothyroidism: Counsel before pregnancy. If already on T4 before detecting pregnancy: Increase L-thyroxine intake by 20-30% immediately + contact caregivers urgently. [e.g. take an extra L-thyroxine dose twice weekly beginning immediately]

MONITORING: TSH ~q4 weeks until ~20 weeks, and at least once ~30 weeks. T4 requirements go up as early as 4-6 weeks of pregnancy, and increase through weeks 16-20, then plateau until delivery. 50 and 85% of LT4-treated hypothyroid women need a dose increase during pregnancy. Target TSH: 0.4-2.5 mU/L throughout pregnancy. Return to preconception T4 dose following delivery, TSH @ 6 weeks.



iodine: MIT and DIT binding to thyroglobulin is inhibited by large doses of Iodine ["Wolff-Chaikoff effect"] (e.g. Amiodarone, KI, radiocontrast agents). Usually transient, but may persist.

Management of amiodarone-induced hypothyroidism

1. Keep amiodarone + T4 replacement to normalize TSH. May require higher-than-normal T4 doses to overcome amiodarone effects.
2. Stopping amiodarone will resolve hypothyroidism unless underlying dysfunction.

Management of myxedema coma [Endocrinol Metab Clin N Am 2006;35;687-698]

1. Measure T4, TSH, cortisol.
2. Before result available, give T4 200-600 μg IV [+/- T3 5-20 μg IV then 10 μg q4h x 24h (only PO in Canada - Cytomel 5 & 25 μg tabs)] then 50-100 μg PO daily.
3. Give 50-100mg IV hydrocortisone q6-12h if cortisol low (some recommending giving to all patients until adrenal function confirmed).
4. Thereafter, T4 50-100 μg IV daily (until taking PO T4) [+/- T3 2.5-10 μg IV/PO q8h] until clinically stable.
5. No trials and no consensus about giving T4 only, T3 only, or combination. BEWARE of CAD and use less T3 or none.

Subclinical Hypothyroidism [AACE/ATA 2012 Guidelines; BMJ 2008;337:a834; JAMA 2006;295:1033-1041; JAGS 2015;63:1663-73]

Definition: TSH 4.5-10 + normal fT4. 4-9% prevalence; 50-80% of these have TPOAb.

Issues: progression to overt hypothyroidism, CAD: best evidence [meta-analysis JAMA 2010;304(12):1365-1374] CHD RR ~1.0 for TSH 4.5-9.9; CHD RR 1.89 [1.28-2.8] for TSH 10-19.9. Similar data for CHD death. No total mortality increase. Age, sex, previous CV disease didn't alter estimates.

Management: **No evidence that treatment alters symptoms or outcomes** (Cochrane review CD003419), particularly CV outcomes. TRUST trial showed no symptom or any other benefit of T4 tx in >65 y/o's x 1year [NEJM 2017;376:2534-2544]. ?Consider treating if pregnant (borderline hypothyroidism may --> fetal neuropsych problems, tx may reduce preterm delivery [Cochrane Database Syst Rev 2010 Jul 7;(7):CD007752]). In elderly: possibly improved BMI, BP [Arch Gerontol Geriatr 2007;44:13-19], but no benefit on cognition [J Clin Endocrinol Metab 2006;91:145–53, 2010;95:3623-32]. If treating, use low-dose T4 (25-75 mcg/d). Regular thyroid monitoring in subclinical hypothyroid patients to detect overt hypothyroidism.

Signs & Symptoms of Excess

Most common: **weight loss, fatigue, heat intolerance, tremor, palpitations**

Skin
- •diaphoresis +/- heat intolerance
- •onycholysis "Plummer's Nails"
- •hyperpigmentation
- •pruritus/hives (in Graves')
- •vitiligo + alopecia areata
- •hair thinning

Cardiovascular
- •palpitations
- •increased cardiac output, increased tissue O2 demand, increased cardiac contractility
- •tachycardia (absent in 40% of elderly hyperthyroid)
- •widened pulse pressure
- •decreased SVR
- •high-output heart failure
- •atrial fibrillation (10-20%)
- •L atrial enlargement
- •mitral valve prolapse
- •low serum TChol & HDL

Eyes
- •stare + lid lag (sclera can be seen above the iris as patient looks downward)
- •proptosis (in Graves') → diplopia → corneal ulceration → optic neuropathy → blindness

Respiratory
- •tachypnea → respiratory muscle weakness
- •dyspnea (hypoxemia + hypercapnia)
- •obstruction d/t goitre
- •asthma exacerbation

GI
- •malabsorption + hypermotility → weight loss
- •diarrhea
- •constipation in elderly
- •dysphagia d/t goitre
- •elevated AlkPhos

Heme
- •normochromic normocytic anemia
- •ferritin and fibrinogen may be elevated
- •ITP or pernicious anemia (in Graves')

GU
- •urinary frequency + nocturia
- •amenorrhea
- •gynecomastia, decreased libido, erectile dysfunction

MSK
- •increased bone resorption → osteomalacia (more in cortical than trabecular bone) → hypercalcemia → parathyroid H inhibition → decreased Ca absorption + decreased calcidiol conversion to calcitriol → osteoporosis
- •"thyroid acropathy" (Graves'): clubbing periosteal bone formation in phalanges & metacarpals
- •proximal muscle weakness
- •myasthenia gravis (in Graves')

Neuro
- •tremor (hands, tongue)
- •hyperactive deep tendon reflexes
- •emotional lability, anxiety, hyperactivity, insomnia, inability to concentrate

Signs & Symptoms of Deficiency

Skin
- -dry, coarse skin
- -puffy facies
- -loss of eyebrows
- -eczema

Cardiovascular
- -bradycardia
- -diastolic HTN
- -fatigue
- -pericardial effusion

Eyes
- -periorbital edema

Respiratory
- -dyspnea on exertion
- -pleural effusion

GI
- -constipation
- -weight gain
- -ascites

GU
- -menorrhagia
- -pubertal delay

MSK
- -growth failure
- -myalgia, cramps
- -weakness
- -bradykinesia
- -carpal tunnel syndrome

Neuro
- -paresthesia
- -depression
- -cognitive dysfunction
- -decreased hearing
- -slow speech
- -sleep apnea

Other
- -cold sensitivity
- -hoarseness
- -galactorrhea
- -hyperprolactinemia
- -tongue enlargement
- -increased LDL & TChol
- -hyponatremia? (Rare, only in severe hypothyroidism. BMJ 2006;332:854)