Thyroid Disease

PES Board Review Course in Pediatric Endocrinology – 2025

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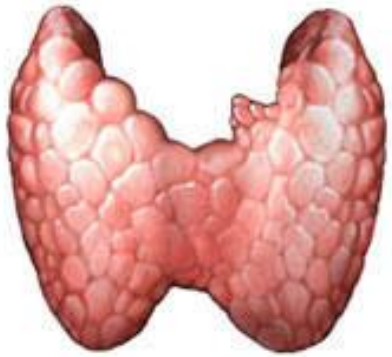
Topics to be covered from ABP outline

- **Diffuse thyroid enlargement**
- **Thyroiditis**
- **Acquired hypothyroidism**
- **Thyroid hormone resistance**
- **Thyroid hormone excess**
- **Thyroxine-binding globulin (TBG) deficiency and excess**

Diffuse thyroid enlargement (goiter)



Normal thyroid growth

- **Thyroid gland increased by about 1 gram per year until the age of about 15 y.o.**
- **Adult thyroid gland is approximately 15 to 20 grams**
- **Rapid increase in thyroid volume occurs normally during puberty with maximum growth rate at 12.5 y.o.**

Diffuse thyroid enlargement

- Chronic lymphocytic thyroiditis (Hashimoto)
- Colloid goiter
- Thyroid hormone resistance
- Subacute or acute thyroiditis
- Graves disease
- Congenital hypothyroidism (dyshormonogenesis)
- Iodine deficiency (endemic goiter)
- Excessive iodine ingestion (Wolff-Chaikoff effect)
- Infiltrative disorders
  - Histiocytosis
  - Cystinosis
  - Neoplasms: lymphoma or teratoma
  - Adults: sarcoidosis and amyloidosis (rare in children)

Evaluation of diffuse thyroid enlargement

- **Lab tests: TSH (a.k.a thyrotropin), T4, thyroid antibodies**
- **Imaging**
  - **Ultrasound**
  - **Thyroid scintigraphy/uptake**
- **Concerning signs/symptoms would lead to additional imaging and evaluation**
  - **Tracheal compression: dyspnea, stridor, cough, choking sensation**
  - **Vocal cord paralysis: dyspnea, hoarseness**

Treatment of euthyroid diffuse thyroid enlargement

- **Conservative management – observation**
- **Surgery**
  - **Pros: rapid resolution, able to examine pathology**
  - **Cons: hypothyroid, hypoparathyroidism, scar, nerve/blood vessel injury (and it's surgery!)**
- **Radioactive iodine**
  - **Pros: decrease in size, no scar**
  - **Cons: not a rapid decrease, radiation-induced dysfunction**
- **Levothyroxine**
  - **Best result if TSH is elevated and positive antibodies, but usually only a small (and often variable) reduction in size**
  - **Controversial: long-term efficacy unknown, cardiac/bone risk**

Thyroiditis

Thyroiditis (= inflammation)

- **Acute suppurative – very, very, very rare**
- **Subacute (de Quervain) – very, very rare**
- **Subacute (lymphocytic) – relatively uncommon**
  - **a.k.a. silent or sporadic**
  - **??? Hashitoxicosis**
- **Chronic – common**
  - **a.k.a. Hashimoto thyroiditis**

Acute (suppurative) thyroiditis

- **Infectious: bacterial (68%) or fungal (15%) etiology (not viral)**
- **Most common route of infection is from a left pyriform sinus fistula**

- **Signs/symptoms: pain (radiating to ear), tenderness, warmth, fever, dysphagia, and dysphonia; antecedent URI; ↑ CRP and ESR; ↑↑ WBC**

- **2/3 with normal TSH – can also see ↑ TSH and ↓ TSH**
- **Ultrasound → abscess, swelling**
- **Treatment: antibiotics and possible surgery (I&D)**

Subacute (de Quervain) thyroiditis

- Viral (e.g. mumps, adeno, EBV, coxsackie, influenza)
- Most common cause of a painful thyroid gland
- Signs/symptoms: viral prodrome (fever, malaise, myalgia), constant tenderness over entire thyroid; ↑ CRP and ESR; normal to mild ↑ WBC
- Biochemical hyperthyroidism (↓ TSH) in about 50%
- Spontaneous and variable remitting inflammation that lasts for weeks to months → hyperthyroid → euthyroid → hypothyroid → euthyroid or hypothyroid (5-30%)
- Treatment: NSAIDs or glucocorticoids

Subacute (lympocytic) thyroiditis

- **Also known as “silent” or “sporadic” thyroiditis in the adult literature and textbooks**
- **Hashitoxicosis???**

- **Transient hyperthyroidism due to lymphocytic invasion and destruction of thyroid tissue**
- **Variable symptoms but generally mild and intermittent**
- **50-60% will have some thyroid enlargement**
- **Hyperthyroidism → euthyroid and/or hypothyroidism**
- **Propensity for transient thyroid abnormalities to recur in affected individuals**

Chronic thyroiditis

- **Chronic lymphocytic thyroiditis = Hashimoto thyroiditis**
- **The most common cause of diffuse thyroid gland enlargement outside of the newborn period**
- **Variable clinical course**
- **Postpartum thyroiditis**
  - **Destructive thyrotoxicosis (presents by 14 weeks postpartum)**
  - **Usually a transient hypothyroidism → development of persistent hypothyroidism in up to 30% of cases**

Acquired hypothyroidism

Etiologies of hypothyroidism

Primary

- Hashimoto
- Iodine deficiency/excess
- Neck irradiation
  - e.g. Wilms, craniospinal
- Drugs
- Syndromes
- Infiltrative processes
- Cystinosis
- Congenital

Secondary (central)

- Hypopituitarism
- Cranial radiation
- CNS process
  - Tumor, infection, injury
- Isolated TSH β gene mutation

Other

- Hepatic hemangioma
  - ↑ type 3 deiodinase

Agents and drugs that may interfere with thyroid function

- **Increased clearance:**
  - Phenobarbital
  - Phenytoin
  - Carbamazepine
  - Oxcarbazepine
  - Rifampin
- **Impaired or disrupted peripheral metabolism:**
  - Glucocorticoids
  - Amiodarone
  - PTU
  - Propranolol
- **Effects on thyroid hormone production and secretion:**
  - Iodine-containing products (anti-septics, betadine, IV contrast, etc)
  - Lithium
  - Amiodarone

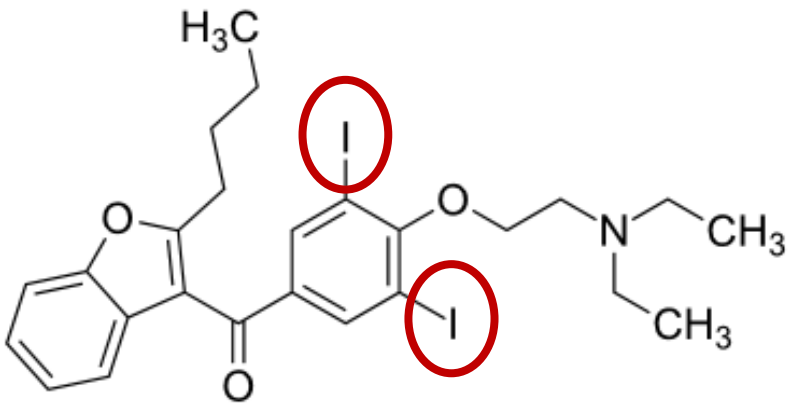
Agents and drugs that may interfere with thyroid function

- **Effects on the hypothalamic-pituitary-thyroid (HPT) axis:**
  - **Decrease TSH**
    - **Dopamine**
    - **Dopamine agonists (bromocriptine, cabergoline)**
    - **Glucocorticoids**
    - **Opiates**
    - **Octreotide**
  - **Increase TSH**
    - **Hypocortisolism (Addison)**
    - **Dopamine receptor blockers (metoclopramide)**

Iodine effects on thyroid function

- **Iodine is the rate-limiting step in thyroid hormone synthesis**
- **#1 cause of hypothyroidism in the world is due to iodine deficiency**
  - **Salt has been iodized in the USA since 1924**
- **Wolff-Chaikoff effect**
  - **Protective mechanism when the body is exposed to excess amounts of iodine**
  - **Inhibits organification of iodine: ↓ T4 and T3 synthesis**
  - **Dose dependent effect that may last weeks or longer → escape**

Amiodarone



- Incidence of thyroid dysfunction: up to 24%
- <u>Hypothyroidism</u>
  - Inhibits the conversion of T4 to T3
  - Inhibits thyroid hormone synthesis and secretion (Wolff-Chaikoff effect)
- Occurs most often during the first year of treatment
- Lipophilic → long half-life (about 100 days)
  - Total body iodine stores do not return to normal for 6 to 9 months after stopping the medication

Amiodarone

- **Hyperthyroidism can also occur but it is less common than hypothyroidism**
- **Occurs on average after about 3 years of treatment**

- **Type 1**
  - **↑ iodine leads to ↑ T4 production**
  - **Underlying autoimmune thyroid disease (+Abs); enlarged nodular thyroid**

- **Type 2**
  - **Inflammatory process causing thyroid damage (↑ IL-6)**
  - **Normal thyroid size; normal ultrasound**

Lithium

- **Hypothyroidism and goiter are the most common thyroid problems in individuals treated with lithium**
  - **Inhibits thyroid hormone synthesis and secretion**
  - **Increased autoimmune thyroid disease**

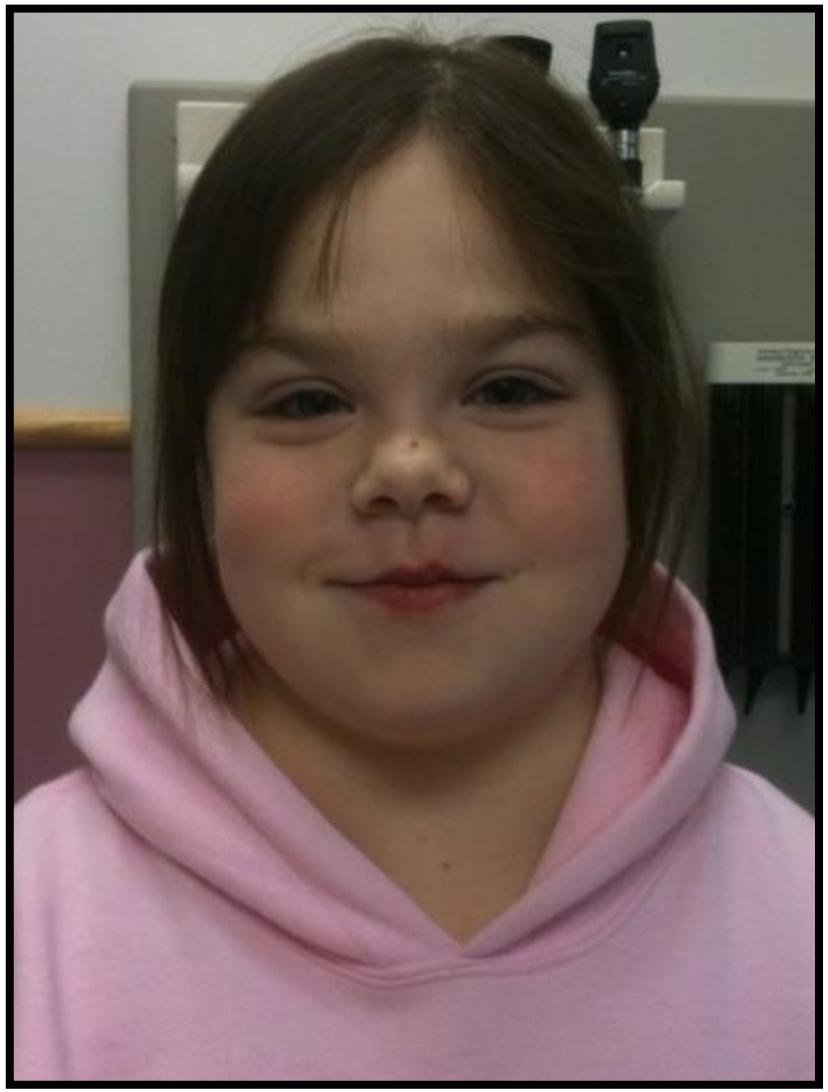
- **Very infrequent occurrence of hyperthyroidism**
  - **Most commonly a transient and painless thyroiditis**
  - **Also reports of induced thyroid autoimmunity**

Cystinosis

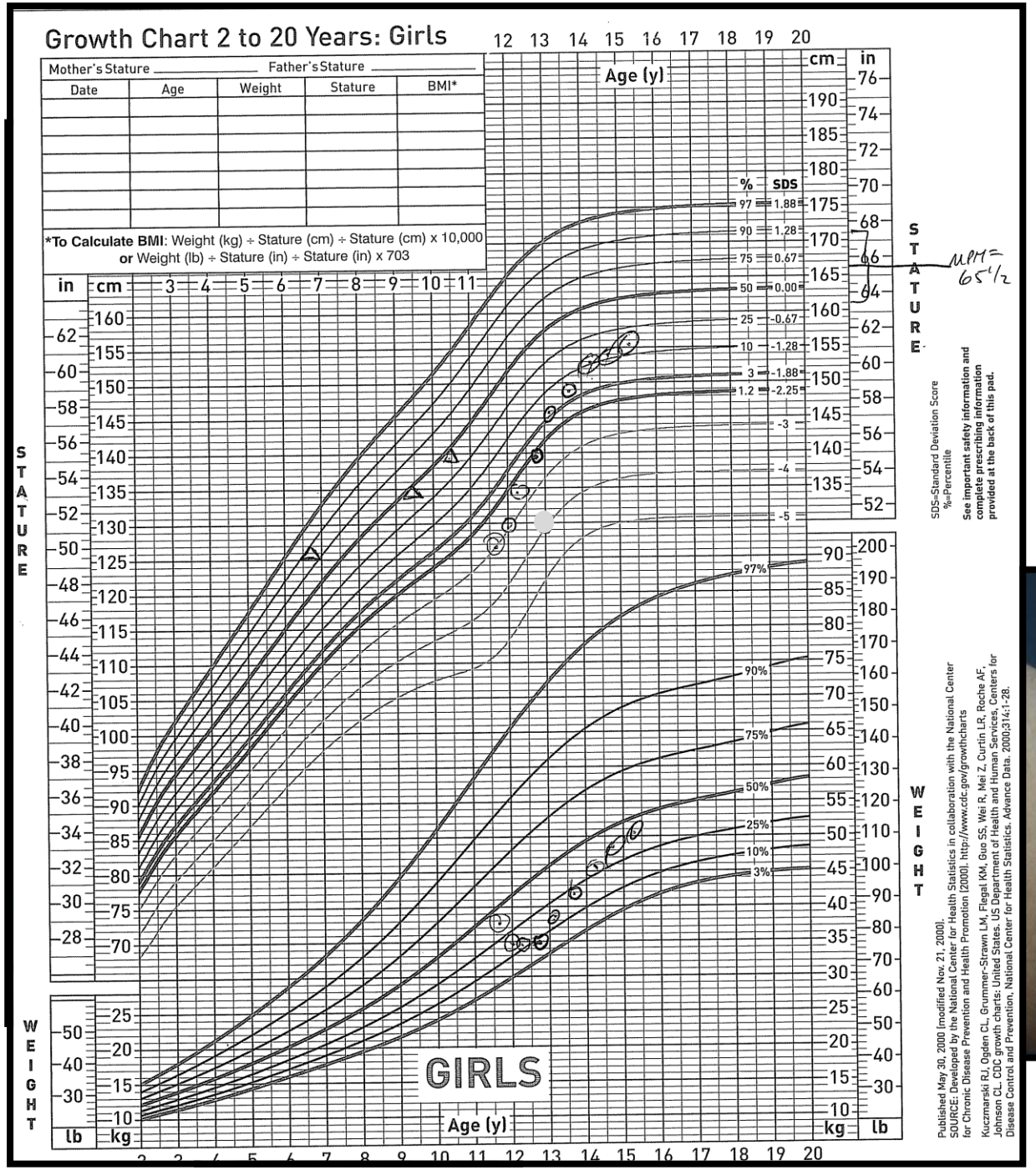
- **Rare autosomal recessive lysosomal storage disease**
- **Most common hereditary cause of renal Fanconi syndrome in children**

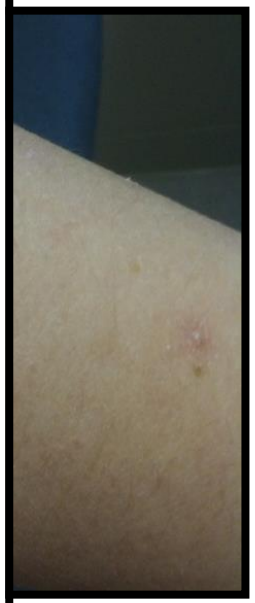
- **Cystine and crystal formation builds up in various tissues**
  - **Thyroid follicular cells → fibrosis and atrophy**

- **Common to see subclinical hypothyroidism in children**
- **Hypothyroidism occurs in >50% of patients by the 2nd decade of life**



11-year-old girl





Clinical and lab findings in acquired hypothyroidism*

- Reduced heart rate and decreased cardiac contractility
- Delayed relaxation phase of DTRs
- Dry skin (↓ sweat and sebaceous gland activity)
- Periorbital puffiness, non-pitting edema (hyaluronic acid)
- Hypercholesterolemia (↑ LDL)
- Hyponatremia (increased total body water)
- Anemia (↓ erythropoietin, ↓ oxygen requirement)
- Elevated creatinine kinase and LDH (from skeletal muscle)
- Reduced GFR
- Elevated liver transaminases

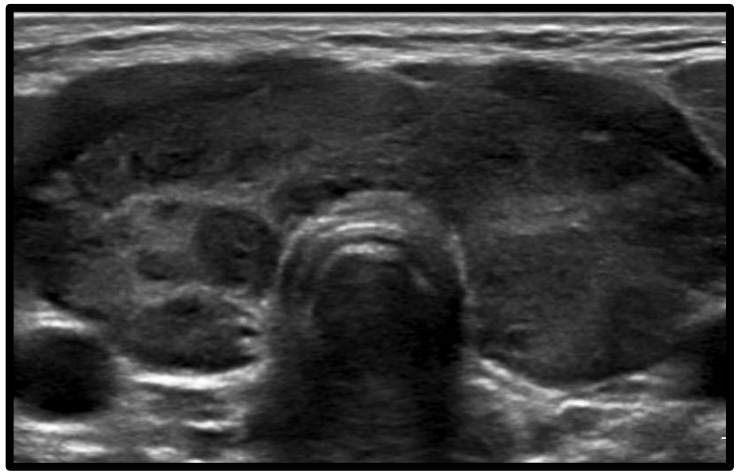
* Clinical features of central hypothyroidism are milder than primary hypothyroidism

Endocrine abnormalities in acquired primary hypothyroidism

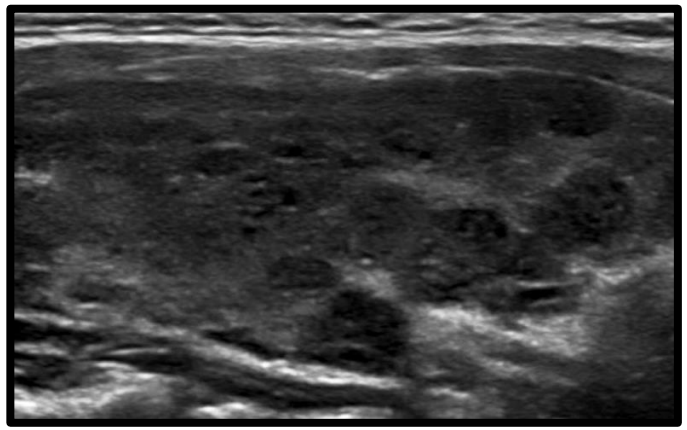
- **Elevated prolactin**
  - **Due to TRH stimulation from the hypothalamus**
- **Delayed puberty / irregular periods**
  - **Altered and blunted LH pulsatility**
  - **Elevated prolactin**
- **Pseudoprecocious puberty (van Wyk-Grumbach syndrome)**
- **Decreased and impaired spontaneous GH secretion**

Exam and imaging in Hashimoto thyroiditis

- **Physical exam**
  - Diffuse enlargement
  - Irregular cobblestone texture
  - Asymmetry (may mimic a nodule)



- **Imaging characteristics**
  - Ultrasound:
    - Diffusely enlarged with heterogeneous echotexture
    - Hypoechoic micronodules (1-6 mm)
  - Nuclear imaging:
    - Early disease can have increased uptake
    - Most common to see decreased, patchy uptake



Patient populations at increased risk for autoimmune thyroid disease

- **Down syndrome (about 40% with + antibodies)**
  - **Prevalence of antibodies increase with age, especially after 6 y.o.**
- **Turner syndrome (about 30% with + antibodies)**
- **Type 1 diabetes mellitus (about 25% with + antibodies)**

Association of Hashimoto with other autoimmune diseases

- **Autoimmune polyglandular (polyendocrine) syndrome, type 1 – *AIRE***
  - **Mucocutaneous candidiasis (1st sign – typically before 5 y.o.; >80%)**
  - **Hypoparathyroidism (usually before puberty or by 10 y.o.; 75-85%)**
  - **Addison disease (usually in adolescence or by 15 y.o.; 60-70%)**
  - **Other features: oophoritis, alopecia, vitiligo, hepatitis, thyroiditis, keratitis**
- **Autoimmune polyglandular (polyendocrine) syndrome, type 2 – polygenic**
  - **Addison disease**
  - **Autoimmune thyroid disease**
  - **Type 1 diabetes**
- **Other: type 1 diabetes, celiac disease, IPEX**

Diagnosis of primary hypothyroidism

- ↑ TSH – treatment indicated when TSH > 10
- Positive antibodies in Hashimoto thyroiditis
  - Thyroid peroxidase (TPO)
  - Anti-thyroglobulin
  - TPO (90%) is more commonly positive than anti-thyroglobulin antibody (50%)
  - About 5-10% may have negative thyroid antibodies
  - Antibodies are not functional – just a marker of inflammation
- Ultrasound
  - Not routinely done in the United States unless there is a palpable nodule, asymmetry, or other clinical concerns

Frequency of positive thyroid antibodies

- **Incidence of thyroid antibodies in the pediatric population is not well characterized**
- **10-12% of the adult population (and >30% of elderly adults) have positive thyroid antibodies**
- **If TSH, T4, and thyroid exam are normal, levothyroxine treatment is not indicated for antibody titer alone**
- **Waxing and waning course**
- **About 25% of those children with a positive thyroid antibody will develop hypothyroidism (TSH > 10) requiring levothyroxine**

Dosage in primary hypothyroidism

- **Levothyroxine (LT4) tablet monotherapy**
  - **Evidence does not support using T3 alone or combination therapy with T4 and T3**
- **Neonates: 10-15 mcg/kg/day**
- **3-6 m.o.: 8-10 mcg/kg/day**
- **6-12 m.o.: 6-8 mcg/kg/day**
- **1-3 y.o.: 4-6 mcg/kg/day**
- **3-10 y.o.: 3-4 mcg/kg/day**
- **10-15 y.o.: 2-4 mcg/kg/day**
- **> 15 y.o.: 2-3 mcg/kg/day**

Evidence to support the above statements is lacking – the more important aspect is consistency and regularity in taking the LT4

Levothyroxine treatment

- **Half-life of LT4 is about 7 days**
- **Wait at least 4 to 6 weeks after a dose adjustment to get to a steady state before rechecking TSH**

- **Goal in primary hypothyroidism is to get the TSH into the normal reference range**
- **Goal in central hypothyroidism is to get the free T4 into the upper half of the reference range (about 1.6 mcg/kg/day)**

- **Absorption can be affected by: soy, fiber, iron, and calcium**

Levothyroxine treatment – prognosis

- **Be aware of ultimate outcome of acquired hypothyroidism, including impact of the disorder on the patient's growth and mental development**

- **Recognize the occurrence of pseudotumor cerebri in some hypothyroid children treated with thyroxine**
- **Be aware that delay in the treatment of acquired hypothyroidism and overzealous replacement therapy may have an adverse effect on ultimate height**
  - **Low dose LT4 and slow normalization of TFTs**
  - **Other interventions have had variable and mixed results**

Thyroid hormone deficiency may develop during treatment of GHD

- **TSH deficiency (central hypothyroidism) may occur after initiation of GH therapy**
- **More likely to occur if brain MRI is abnormal and/or baseline T4 or free T4 are on the lower side**
- **Thought to be due to increased somatostatin secretion in response to pulsed doses of GH**
- **Check TFTs within 3-4 months after starting GH injections and then annually, or sooner if poor growth velocity and patient is compliant with the GH injections**

Thyroid hormone resistance

Thyroid hormone resistance (a.k.a. RTH)

- **Mutations in the thyroid hormone receptor β gene**

- **Precise incidence is unknown**
- **Estimated prevalence of 1 in 40,000**

- **Autosomal dominant inheritance**
- **Rare report of an autosomal recessive inheritance**
- **De novo mutation occurs about 22% of the time**
- **15% of individuals with RTH do not have a detectable mutation in the TRβ gene**

Thyroid hormone resistance (a.k.a. RTH)

- TRα1 – CNS, heart, skeletal muscle
- TRα2 – widely distributed in tissues
- TRβ1 – liver, kidney
- TRβ2 – pituitary, hypothalamus

- Pituitary resistance to thyroid hormone (PRTH) vs. Generalized resistance to thyroid hormone (GRTH)
- Old terms – same condition with same mutations
  - Due to the subjective nature of thyroid symptoms and the poor specificity of thyroid signs
  - Hyperthyroidism and hypothyroidism can coexist depending on tissue TR

Clinical findings – RTH

- **Goiter (66-95%)**
- **Tachycardia (33-75%)**
- **ADHD (40-60%)**
- **Hyperkinetic behavior (33-68%)**
- **Emotional disturbances (60%)**
- **Less common: learning disability, developmental delay, short stature, low BMI**
- **Positive family history**
- **Labs: ↑ free T4, ↑ T3, and non-suppressed TSH**

Diagnostic approach – RTH

- **Confirm elevated free T4 by equilibrium dialysis with a non-suppressed TSH**
  - **Eliminate lab assay interference: heterophile antibodies, protein binding abnormality**
- **Check TFTs in first-degree family members**
- **Sequence TRβ gene**
- **If negative gene testing and normal TFTs in first-degree family members, then**
  - **Check pituitary glycoprotein α-subunit (r/o TSH adenoma)**
  - **T3 suppression 3-day test → blunted and incomplete TSH suppression with supraphysiologic doses of T3 with negative genetic testing points to nonTR-RTH**

Treatment – RTH

- Compensated “euthyroid” state – may not need any treatment
- Recognize the correct diagnosis and avoid unnecessary treatment (e.g. anti-thyroid drugs)
- Atenolol (not propranolol) – for tachycardia, palpitations
- Single large dose of T3 every other day – may be used to reduce thyroid size (surgery is not effective)
- LT4 treatment of infants is controversial and done when
  - Marked elevation of TSH
  - History of adverse events in other affected family members
  - Failure to thrive and/or growth retardation
  - Developmental delays

Thyroid hormone excess

TSH receptor antibodies

- **2 types of antibodies:**
  1) **Stimulating → bind to TSH receptor on thyroid follicular cells and lead to autonomous thyroid hormone production**
  2) **Inhibitory → bind to TSH receptor and block intracellular signaling**
- **Radioreceptor assays**
  - **TSH receptor antibody (TRAb) or TSH-binding inhibitory immunoglobulin (TBII)**
  - **Measures both stimulating and blocking antibodies**
- **Bioassays**
  - **Stimulation of adenyl cyclase in a cell line transfected with the TSH receptor → thyroid stimulating immunoglobulin (TSI)**
  - **Measures only stimulating antibodies**

Neonatal Graves disease

- **Prevalence of neonatal hyperthyroidism in infants of mothers with Graves disease occurs between 1.5-2.5% (one study reported up to 20%)**

- **TRAb are IgG antibodies that readily cross the placenta**
- **The higher the maternal TRAb, the more likely neonatal Graves disease will occur**
  - **Greater than 3.3x the upper limit: 100% sensitive, 43% specific**

- **TRAb should be checked between 20-24 weeks gestation to determine if the fetus is at risk**

Neonatal Graves disease – fetus

- **Fetal hyperthyroidism is most commonly detected in the 3rd trimester but can be apparent at the 20 week ultrasound:**
  - **Goiter (could be from hypothyroidism or hyperthyroidism)**
  - **Increase thyroid vascularity**
  - **Tachycardia**
  - **Heart failure with non-immune hydrops**
  - **Preterm birth**
  - **Advanced skeletal maturation**
  - **Craniosynostosis**

Neonatal Graves disease – presentation

- Goiter +/- tracheal compression
- Low birth weight / IUGR, poor weight gain, feeding difficulties, diarrhea
- Stare, periorbital edema, small fontanelle
- Hyperthermia, warm/moist skin, irritability
- Tachycardia, heart failure, hypertension, tachypnea
- Hepatomegaly, splenomegaly, cholestasis
- Thrombocytopenia, hyperviscosity

  → can be confused with sepsis or congenital viral infection
- Mortality rate: up to 20%

Neonatal Graves disease – screening and course

- **Overt hyperthyroidism may be present at birth**
- **Delayed presentation occurs due to TSH-receptor blocking antibodies or maternal anti-thyroid drugs**
- **>95% of affected infants present between 1 and 29 days of life, and most present within the first 2 weeks**

- **Check TFTs at 3 to 5 days of life or sooner if clinical concerns**
- **If normal, repeat TFTs at 10 to 14 days of life**
- **Clinical assessment at 1 month, 2 months, and 3 months to identify the small population of delayed presentation**

Neonatal Graves disease – treatment

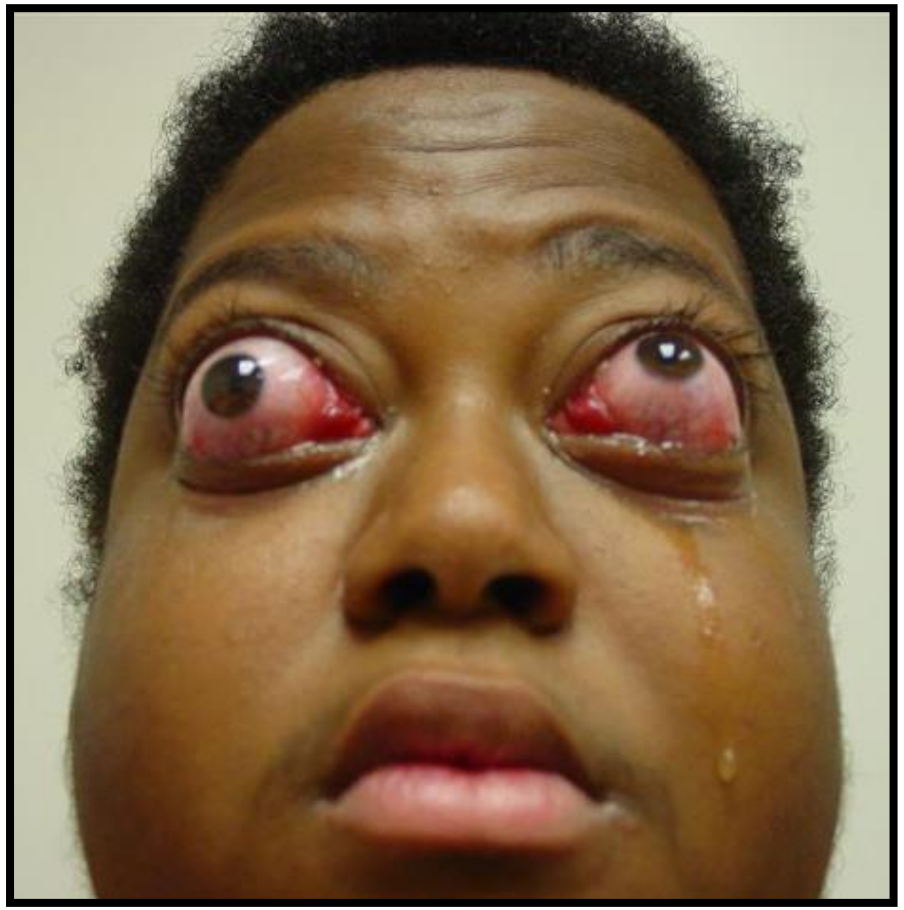
- Treatment of asymptomatic neonates is controversial
- Options for treatment if symptomatic are
  - Methimazole
  - Propranolol
  - Potassium iodide oral solution
  - Prednisolone
- Check labs weekly until stable then every 2 weeks
- Wean methimazole dose when free T4 is in normal range
- Treatment duration is typically 1 to 2 months (but may last longer depending on TRAb level)

Signs/symptoms of Graves disease in children

- **Goiter (>95%)**
- **Increased linear growth**
- **Weight loss, hyperphagia, loose stools**
- **Tachycardia, palpitations, hypertension, wide pulse pressure**
- **Diaphoresis**
- **Tremors, tongue fasciculations, milk maid's grip**
- **Jittery, anxious, "ants in their pants"**
- **Fatigue, exercise intolerance**
- **Irregular menses**

Signs/symptoms of Graves disease in children

- **Eye disease is less common in children and adolescents compared to adults**
  - **Lid lag**
  - **Corneal dryness**
  - **Erythema**
  - **Tearing**
  - **Strabismus**
  - **Vision loss**



Initial treatment

- β blockers are used to treat the hyperthyroid symptoms

- Propranolol
  - Blocks T4 → T3 conversion
  - Non-selective – blocks β1 and β2
- Atenolol
  - Once-a-day
  - Cardio-selective (β1)
- Metoprolol XR
  - CNS penetration – useful if having psychosis, anxiety
  - Cardio-selective (β1)

Medical treatment

- PTU is contraindicated due to hepatotoxicity
- Methimazole (MMI)
  - Dose is 0.1-1.0 mg/kg/day (typical dose: 0.2-0.5 mg/kg/day)
  - Rash is most common adverse event (20%)
  - Bone marrow suppression and liver toxicity are most severe adverse events (<1%)
  - Check CBC and LFTs before starting treatment
- After MMI for 12-24 months, remission rate is 20-30%
- Low chance of remission if large thyroid, young age, more severe presentation (high free T4 and TRAb)

Definitive treatment

- **Indicated if adverse effects from methimazole, unable to achieve remission, or patient preference**
- **Goal is to achieve permanent hypothyroidism**
- **Options:**
  - **Radioactive iodine (I-131)**
  - **Surgery**

Radioactive iodine (I-131) ablation

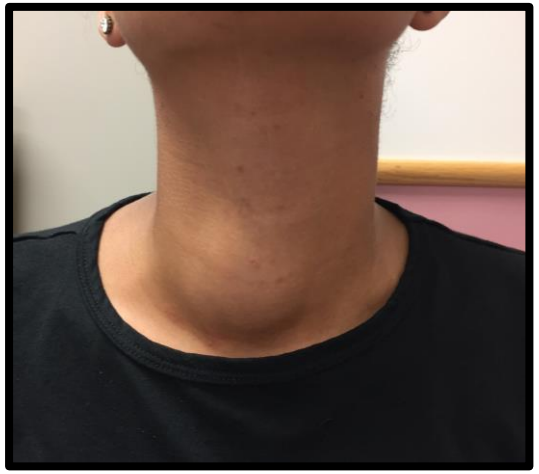
- **Not recommended in children < 5 y.o.**
- **Considered safe in children 5-10 y.o. if dose is < 10 mCi of I-131**
- **Safe in children > 10 y.o.: >150 µCi of I-131 per gram of thyroid tissue for ablation**
- **Theoretical risks of cancer; long-term data appears reassuring if complete ablation occurs**
- **Reasons to do RAI: family choice (no scar), minimal to no eye disease, no thyroid nodule, goiter < 80 grams**
- **Important to remember that TRAb can persist for years in a subset of women → risk of neonatal Graves**

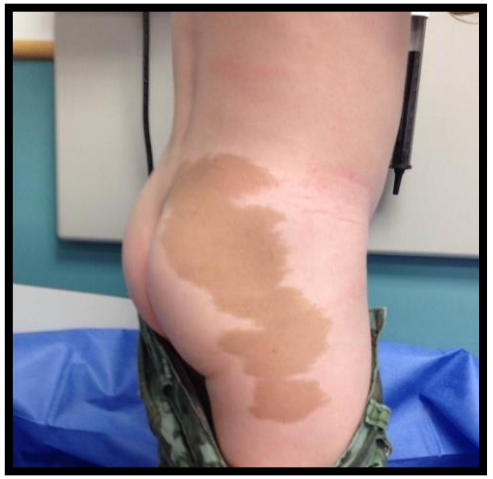
Surgery – thyroidectomy

- **Important to achieve a euthyroid state before surgery**
  - **MMI given for 1-2 months before operation**
- **Potassium iodide (KI) given in the preoperative period to reduce gland vascularity and diminish blood loss**
  - **1-2 drops TID for 10 days before surgery**
- **Reasons to do surgery: family choice, age < 5-10 y.o., access to high volume and experienced surgeon, significant eye disease, goiter > 80 grams (>3-4x enlarged)**
- **Risks: transient or permanent hypoparathyroidism (hypocalcemia), recurrent laryngeal nerve injury, hematoma, permanent scar**

Other (rarer) causes of hyperthyroidism

- Autonomously functioning (hot) nodule
- Hashitoxicosis
- Familial non-autoimmune hyperthyroidism
- McCune-Albright syndrome
- Thyroid hormone resistance (RTH)
- Acute (suppurative) thyroiditis
- Subacute (viral) thyroiditis
- TSH adenoma → ↑ pituitary glycoprotein α-subunit
- Ingestion of ground beef (inclusion of strap muscles)
- Factitious → ↓ thyroglobulin level





Familial non-autoimmune hyperthyroidism

- a.k.a. Hereditary toxic thyroid hyperplasia
- Due to an activating mutation of the TSH receptor
- Autosomal dominant
- Hyperthyroidism with variable age at onset (infancy to adulthood, even within same family)
- Hyperplastic goiter of variable size but with steady growth
- Negative thyroid autoantibodies

Differential diagnosis of hyperthyroidism

	Graves disease	Hashitoxicosis	(Sub)acute thyroiditis	LT4 ingestion
Thyroid exam	Non-tender goiter	Non-tender goiter	Tender goiter	No goiter, no tenderness
TSH	↓	↓	↓	↓
Free T4, T3	↑↑	Normal or ↑	Normal or ↑	↑
Thyroglobulin	↑	Variable	Variable	↓
Antibodies	+ TRAb + TPO +/- anti-TG	+ TRAb (10%) + TPO + anti-TG	Negative antibodies	Negative antibodies
Uptake scan	↑	↓ (usually)	↓	↓

Thyroxine-binding globulin

Thyroxine-binding globulin (TBG)

- **Very little thyroid hormone is free and unbound**
  - **99.97% of T4 is bound**
  - **99.7% of T3 is bound**
  - **Therefore, <0.3% of thyroid hormone is “free”**

- **Most thyroid hormone is bound to proteins**
  - **70-80% to TBG**
  - **15-25% to transthyretin (thyroxine-binding prealbumin)**
  - **<10% to albumin**
  - **Potency of binding to T4: TBG >> transthyretin >>> albumin**

Factors affecting TBG levels

Decreased TBG

- Inherited
- Androgens
- Glucocorticoids
- Severe illness
- Hepatic failure
- Nephrotic syndrome
- Nicotinic acid
- L-asparaginase

Increased TBG

- Inherited
- Pregnancy
- Estrogens
- Hepatitis
- Porphyria
- Opioids (e.g. heroin, methadone)
- Mitotane
- SERMs (e.g. tamoxifen)

Euthyroid sick syndrome

- Significant decrease in TBG
- ↓ in type 1 deiodinase (T4 → T3)
- ↑ in type 3 deiodinase (T4 → rT3)
- Labs in severe illness can look similar to central hypothyroidism:

	Mild illness	Moderate illness	Severe illness
Total T3	↓	↓↓	↓↓↓
Free T4	Normal	Normal to ↓	↓
rT3	↑	↑↑	↑↑↑
TSH	Normal	Normal to ↓	↓

- TSH will rise during the recovery phase

TBG deficiency – inherited

- X-linked condition
- Partial (1 in 4000) or complete (1 in 15,000)
- Heterozygous males are more frequently detected
- Depending on X inactivation, females may have normal, partial, or complete deficiency

- T4 and T3 levels low, TSH is normal, free T4 and free T3 are normal, high T3 uptake (T3U)
- Benign condition → no treatment needed

T3U = 1 / TBG

TBG excess – inherited

- **X-linked condition**
- **Estimated to occur in 1 in 25,000**

- **T4 and T3 levels elevated, TSH is normal, free T4 and free T3 are normal, low T3 uptake (T3U)**

T3U = 1 / TBG

- **Like TBG deficiency, it is a benign condition → no treatment needed**

Familial dysalbuminemic hyperthyroxinemia

- **Genetic variant of albumin resulting in a marked increased affinity for T4 (but not T3)**
- **Mutation in *ALB* (albumin) gene**
- **Autosomal dominant**
- **Prevalence: 1 in 10,000**

- **Normal TSH, normal T3, elevated T4**
- **Normal T3U**
- **Normal free T4 by equilibrium dialysis – may have high direct free T4 due to lab artifact**

ABP outline – handout

- **Additional ABP specifications and information are contained in the handout**