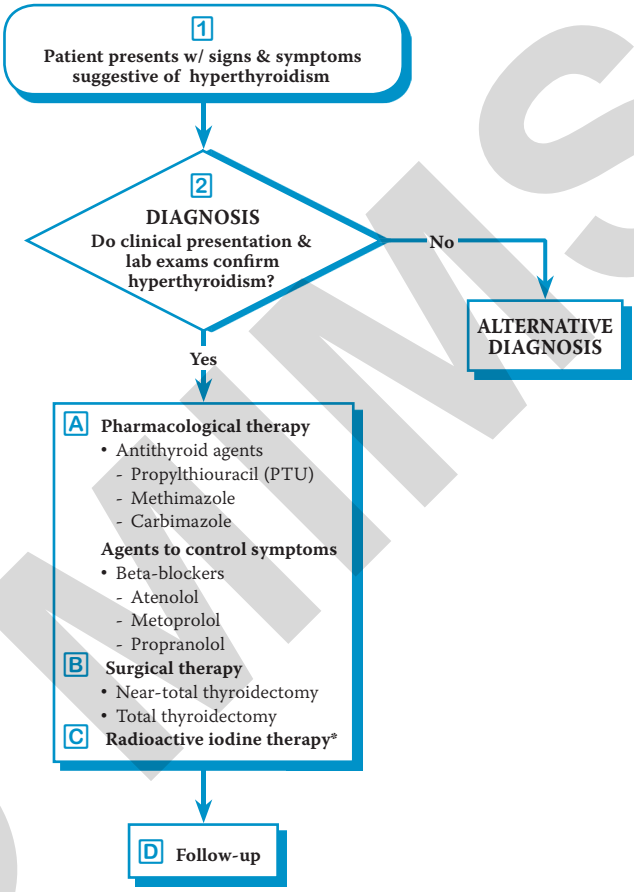
Hyperthyroidism (1 of 6)



*For patients >10 years of age

1 HYPERTHYROIDISM

- Overactivity of the thyroid gland resulting in excessive production of thyroid hormones
- Symptoms are of gradual onset
- Earliest signs may be emotional lability & motor hyperactivity; decline in school performance may also be noted

Causes

- Autoimmune - Graves' disease (most common cause)
- Inappropriate stimulation by trophic factors
- Passive release of preformed thyroid hormone stores in response to infections, trauma, or other offensive factors inside the body
- Extra-thyroidal sources
  - Exogenous - iatrogenic thyrotoxicosis (eg Amiodarone, Lithium, tyrosine kinase inhibitor therapy)
  - Endogenous - metastatic thyroid cancer, TSH-secreting adenoma, choriocarcinoma

Signs & Symptoms

- Irritability, insomnia, altered mood
- Sweating, heat intolerance
- Palpitations
- Fatigue
- Weight loss despite increased appetite
- Tremor
- Goiter
- Palpitations, tachycardia
- Eyelid lag or retraction, exophthalmos which is usually mild

Thyroid Storm or Thyroid Crisis: An acute life-threatening exacerbation of hyperthyroidism

- Signs & symptoms include high fever, changes in sensorium, restlessness, severe tachycardia & arrhythmia
- May be precipitated by trauma, infection, dehydration

2 DIAGNOSIS

History

- A comprehensive history should be elicited
- Most patients have positive family history of some form of autoimmune thyroid disease

Physical Exam

- Weight, height & blood pressure
- Heart rate, cardiac rhythm, apex beat, & respiratory rate
- Inspect & auscultate the neck (check size, nodule, texture of goiter; thyroid bruit)
- Ocular & lymphatic examination
  - Combination of ophthalmopathy & hyperthyroidism is suggestive of Graves' disease
- Dermatologic examination (eg excessive sweating, onycholysis, vitiligo, alopecia)
- Neurologic exam: Presence of tremors, proximal muscle weakness

Lab Exam

- Obtain baseline CBC which includes WBC count w/ differential, & liver profile (ie serum alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase, bilirubin)

Serum Thyroid Stimulating Hormone (TSH) Levels

- Recommended as initial diagnostic exam for patients suspected to have hyperthyroidism
- Serum TSH measurement is highly sensitive & specific for the evaluation of hyperthyroidism
- Thyroid stimulating hormone (TSH) levels are decreased in patients w/ hyperthyroidism
- TSH receptor stimulating autoantibodies titers are elevated in Graves' disease w/ 95% sensitivity & 96% specificity
  - Not routinely measured

Thyroxine (T_4) Levels

- Measure both total & free serum T_4 levels
- Free T_4 improves diagnostic sensitivity/specificity when combined w/ measured TSH levels

Triiodothyronine (T_3) Levels

- Measure both total & free T_3 levels; total T_3 measurement preferred for diagnostic purposes
- T_3 levels may be more elevated than T_4

Others

- T_4 binding globulin (TBG), transthyretin (TTR)

Imaging Procedures

Ultrasound

- Useful in evaluating the size & shape of the thyroid, especially in large glands

Radioactive Iodine Uptake (RAIU) Test

- Recommended to determine the cause of hyperthyroidism
- Usually normal or elevated in the following: Graves' disease, toxic adenoma, toxic multinodular goiter, trophoblastic disease, TSH-producing pituitary adenoma, T_3 receptor mutation
- Near-absent uptake w/ RAIU usually seen in the following: Silent thyroiditis, Amiodarone-induced thyroiditis, de Quervain's thyroiditis, iatrogenic thyrotoxicosis, struma ovarii

2 DIAGNOSIS (CONT'D)

Imaging Procedures (Cont'd)

Thyroid Scan

- Recommended for patients w/ presence of thyroid nodularity

Disease Severity

Overt Hyperthyroidism

- Increased T3, T4 levels, subnormal/undetectable TSH
- Adrenergic manifestations are often more pronounced (eg tachycardia, anxiety, tremor)

Subclinical Hyperthyroidism

- Normal T3, T4 levels, low/undetectable serum TSH
- Milder form of hyperthyroidism

A PHARMACOLOGICAL THERAPY

Antithyroid Agents

- Carbamizole & Methimazole are considered 1st-line treatment
- 2 methods in treating hyperthyroid patients
  - Dose titration: Dose is reduced & titrated against thyroid function tests to achieve a euthyroid state
  - Block & replace regimen: Combination therapy w/ thyroid preparation (eg Levothyroxine) may be considered in patients inadequately controlled by single-dose Carbamizole or Methimazole therapy, or in noncompliant patients
- **Effects:** About 25% of patients remain euthyroid ≥5 years after antithyroid treatment
  - Remission is most likely to occur in patients w/ a small thyroid gland (<2.5x normal size for age), children & adolescents >13 years old, Caucasian, serum TRAb levels less than normal or low T4 levels at diagnosis
  - Relapse usually appears within 3-6 months after stopping the therapy
- Usually takes 3-6 weeks for clinical response to be noticeable
  - 3-4 months to have adequate control
  - May use beta-blockers to control symptoms during this period, but not always needed

Carbimazole

- Inhibits thyroid hormone biosynthesis by decreasing iodide oxidation & iodination of tyrosine
- Recommended as first-line antithyroid treatment in pediatric patients
- Fewer tablets are needed for initial treatment compared w/ PTU

Methimazole

- Methimazole is preferred over PTU because of less adverse effects
  - 10-fold more potent on weight basis than PTU
- Recommended as first-line antithyroid treatment in pediatric patients

Propylthiouracil (PTU)

- Blocks the conversion of T_4 to T_3 in thyroid gland & peripheral tissues, also inhibits thyroid hormone biosynthesis by decreasing iodide oxidation & iodination of tyrosine
- May be considered in patients w/ minimal response to Carbamizole or Methimazole therapy & opposed to surgical or radioactive iodine treatment, or patients w/ thyroid storm
- Patients/caregivers should be informed of the potential to develop irreversible hepatic dysfunction w/ long-term PTU therapy
  - Obtaining a written consent prior to initiation of PTU therapy is advised

Symptomatic Management

Beta-Blockers

- Eg Propanolol, Atenolol, Metoprolol, Nadolol
- Recommended for symptomatic treatment of hyperthyroidism especially in children w/ heart rate of >100 bpm
- Contraindicated in hyperthyroidism patients w/ bronchospastic asthma
  - Nadolol may be given to asthmatic hyperthyroidism patients w/ mild COPD, symptomatic Raynaud's phenomenon, or those whom heart rate control is essential
- Atenolol is the most used beta-blocker because of its cardioselective property, thus less risk for bronchospasm
- Esmolol is preferred over other beta-blockers for older ICU patients w/ thyroid storm/severe thyrotoxicosis

B SURGICAL THERAPY

- Patients may undergo near-total or total thyroidectomy
- Aims to induce hypothyroidism & subsequently balancing thyroid levels w/ thyroid hormone replacement
- **Effects:** Up to 97% cure rate when performed by experienced surgeons

Not all products are available or approved for above use in all countries.
Specific prescribing information may be found in the latest MIMS.

B SURGICAL THERAPY (CONT'D)

- Indications:
  - Sufficient cooperation for medical therapy is not possible
  - Adequate trial of antithyroid agents has failed to cause permanent remission
  - Intolerance to severe side effects of antithyroid drugs
  - Large thyroid gland size (>80 g)
  - Need for immediate disease control
  - <5 years of age
  - For very young patients intolerant to radioactive iodine therapy
- **Potential complications:** Hypoparathyroidism, recurrent laryngeal nerve paralysis, hemorrhage, hypocalcemia
- Iodine therapy rather than surgery is more advisable for patients w/ thyroid enlargement of >80 g

Prior to Surgery

- Restoration of euthyroidism
  - Antithyroid drug treatment over 1-2 months prior to surgery
  - Iodide (eg saturated solution of potassium iodide) is added in the regimen x 10 days prior to surgery; given to decrease the vascularity of the thyroid gland

Permanent Hypothyroidism

- If patients become hypothyroid, T_4 replacement may be considered

C RADIOACTIVE IODINE THERAPY

- Effective & relatively safe in patients >10 years
  - May be considered in patients 5-10 years old but caution during duration of therapy is recommended
- Main goal is to induce hypothyroidism; patients may expect long-term thyroid replacement w/ T_4
- May be considered in patients who relapse after medical therapy
- A single therapeutic dose of RAI 200-300 μCi/g of thyroid tissue is recommended
- Consider pretreatment w/ β-adrenergic blockade & antithyroid agents in asymptomatic patients w/ Graves' disease at increased risk for complications caused by exacerbation or worsening of hyperthyroidism
- Frequency of radioactive iodine therapy is reduced due to theoretical risk of malignancy or genetic damage
- Instructions on radiation safety precautions immediately following treatment
  - Close & prolonged physical contact w/ other people should be avoided for 3 days
  - Caregiver is advised to have the patient take a break from daycare or school for 2 weeks

TREATMENT - OPHTHALMOPATHY

- Usually resolves gradually & independently of hyperthyroidism
  - May resolve when patient becomes euthyroid
- Some symptoms may not resolve especially if the symptoms are caused by autoimmune reaction against fibroblasts or muscles of the orbit
- May be treated w/ high-dose Prednisone
- Surgical decompression of orbits or orbital radiotherapy may also be done

D FOLLOW-UP

- Thyroid function monitoring (free T4, total T3, TSH) is advised for the following:
  - Two to 6 weeks after initiation of antihyroid drug therapy, again at 4-6 weeks, then every 2-3 months once dose has been stabilized
  - Lifelong monitoring for all patients previously prescribed w/ antithyroid drug therapy
  - Monthly monitoring after completion of radioactive iodine therapy
- Doses of antithyroid medications should be discontinued or titrated after 1-2 years of continuous treatment, to assess for disease remission
- Instruct the parents/guardians of patients to immediately report signs of liver dysfunction (jaundice, pruritus, rash, anorexia, right upper quadrant pain, light-colored stool, dark urine)
- Consider radioactive iodine therapy or surgery in patients on antithyroid therapy (Methimazole) for >1-2 years
- Relapse after discontinuation of therapy occurs in 3-47% of pediatric population
  - Studies show that relapse usually occurs within 1 year after treatment discontinuation

Dosage Guidelines

ANTITHYROID AGENTS

Drug	Dosage	Remarks
Carbimazole	**Neonates-<12 yr:** **Initial dose:** 750 mcg/kg PO 24 hrly **Max dose:** 30 mg/day **12-18 yr:** **Initial dose:** 30 mg PO 24 hrly May adjust dose as needed	**Adverse Reactions** • GI effects (N/V, abdominal discomfort, loss of taste); Hematologic effects (agranulocytosis, aplastic anemia, granulocytopenia, thrombocytopenia, hypothrombinemia); Hepatic effects (jaundice, hepatic necrosis, hepatitis, hepatotoxicity); Dermatologic effects (rash, pruritus, skin pigmentation, abnormal hair loss); Other effects (systemic lupus erythematosus-like syndrome, urticaria, fever, arthralgia, neuritis, edema, vertigo) • Most common during the 1st 2 mth of treatment • PTU has been associated w/ greater risk of hepatitis or asymptomatic liver damage than other antithyroid agents **Special Instructions** • Educate patient to report symptoms of agranulocytosis (eg sore throat, fever, mouth sores) immediately to healthcare provider • If agranulocytosis is suspected, drug must be stopped until CBC rules out agranulocytosis • Thiamazole: Additional thyroid hormone may be required • Carbimazole: Doses are adjusted according to response. Higher doses may be needed for thyrotoxicosis
Methimazole (Thiamazole)	**Initial dose:** 0.4 mg/kg/day PO divided 8 hrly **Maintenance dose:** 0.2 mg/kg/day PO divided 8 hrly	
Propylthiouracil (PTU)	**Initial dose:** **Neonates:** 2.5-5 mg/kg PO 12 hrly **1 mth-1 yr:** 2.5 mg/kg PO 8 hrly **1-5 yr:** 25 mg PO 8 hrly **5-12 yr:** 50 mg PO 8 hrly **12-18 yr:** 100 mg PO 8 hrly	

BETA-BLOCKERS[1]

Drug	Dosage	Remarks
Atenolol	**Initial dose:** 0.8-1 mg/kg PO once daily **Max dose:** 2 mg/kg/day (up to 100 mg/day)	**Adverse Reactions** • CV effects (heart failure, 2nd/3rd degree AV block); GI effects (nausea, constipation, diarrhea); CNS effects (headache, dizziness, insomnia, confusion, depression, paraesthesia); Other effects (bronchospasm, cold extremities, fatigue, dyspnea, lethargy, impotence, nightmares) **Special Instructions** • Abrupt withdrawal of the drug should be avoided, should taper over 1-2 wk • Contraindicated in patients w/ sinus bradycardia, >1st degree AV block, cardiogenic shock, acute unstable heart failure • Use w/ caution in patients w/ heart failure, variant angina, diabetes mellitus, hepatic/renal dysfunction

[1]Many beta-blockers are available. Specific prescribing information may be found in the latest MIMS.

All dosage recommendations are for children w/ normal renal & hepatic function unless otherwise stated.
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Dosage Guidelines

BETA-BLOCKERS[1] (CONT'D)		
Drug	**Dosage**	**Remarks**
Metoprolol	25-50 mg PO 6 hrly	**Adverse Reactions** • CV effects (palpitation, bradycardia); GI effects (nausea, constipation, abdominal pain, diarrhea); CNS effects (headache, dizziness); Other effects (postural disorders, cold hands & feet, fatigue, dyspnea) **Special Instructions** • Abrupt withdrawal of the drug should be avoided • Use w/ caution in patients w/ history of asthma, AV conduction disorders, pheochromocytoma, cardiac decompensation • Contraindicated in patients w/ 2nd or 3rd degree AV block, unstable decompensated heart failure, cardiogenic shock, marked sinus bradycardia, sick sinus syndrome, peripheral arterial circulatory disorder, <45 bpm heart rate, >0.24 sec PQ interval, <100 mmHg systolic BP
Propranolol	**1 mth-18 yr:** 250-500 mcg/kg PO 6-8 hrly **Max dose:** 4 mg/kg/day	**Adverse Reactions** • Fatigue, bradycardia, hypotension, heart failure, bronchospasm, GI disturbances **Special Instructions** • Abrupt withdrawal of the drug should be avoided, should taper over 1-2 wk • Contraindicated in patients w/ history of asthma or bronchospasm, cardiovascular disease

[1]Many beta-blockers are available. Specific prescribing information may be found in the latest MIMS.

INORGANIC IODIDES		
Drug	**Dosage**	**Remarks**
Potassium iodide (KI)	**Presurgery:** 250 mg PO 8 hrly x 10-14 days	**Adverse Reactions** • Hypersensitivity reactions (rash, urticaria, angioedema, eosinophilia, lymphadenopathy); GI effects (metallic taste, toothache & sore gums, increased salivation); Pulmonary effects (pulmonary edema, dyspnea, bronchospasm); Other effects (insomnia, impotence, headache, depression) **Special Instructions** • Dilute Lugol's soln w/ milk, water or fruit juice to avoid gastric disturbance • Contraindicated in patients w/ acute bronchitis • May be taken w/ meals to minimize gastric irritation
Strong iodine soln (Lugol's iodine soln)	**Presurgery:** 0.1-0.3 mL (3-5 drops) PO 8 hrly x 10-14 days	

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Please see the end of this section for the reference list.