Thyrotoxicosis

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- In general***, thyrotoxicosis can occur if***
- (i) the thyroid is excessively ***stimulated by trophic factors***;

- (ii) constitutive ***activation of thyroid hormone synthesis and secretion*** occurs, leading to autonomous release of excess thyroid hormone;

- (iii) thyroid ***stores of preformed hormone are passively released*** in excessive amounts owing to autoimmune, infectious, chemical, or mechanical insult; or
- (iv) there is ***exposure to extrathyroidal sources*** of thyroid hormone, which may be either endogenous (struma ovarii, metastatic differentiated thyroid cancer) or exogenous (factitious thyrotoxicosis).

- Hyperthyroidism is generally considered ***overt or subclinical***, depending on the ***biochemical severity of the hyperthyroidism***, although in reality the disease represents a continuum of overactive thyroid function.

- ***Overt hyperthyroidism*** is defined as a ***subnormal*** (usually undetectable) serum thyrotropin (TSH) with ***elevated serum levels*** of triiodothyronine (***T3***) and/or free thyroxine estimates (***free T4***).

- ***Subclinical hyperthyroidism*** is defined as ***a low or undetectable serum TSH*** with ***values within the normal reference range for both T3and free T4.***

- Both overt and subclinical disease may lead to characteristic ***signs and symptoms***, although subclinical hyperthyroidism is usually considered milder.

- ***Endogenous hyperthyroidism*** is most commonly due to ***GD or nodular thyroid disease.***
- ***GD*** is an autoimmune disorder in which ***thyrotropin receptor antibodies (TRAb) stimulate the TSH receptor,*** increasing thyroid hormone production and release.

- The development of ***nodular thyroid disease*** includes ***growth of established nodules,*** new nodule formation, and development of autonomy over time .

- In TAs, ***autonomous hormone production*** can be caused by ***somatic activating mutations of genes*** regulating thyroid growth and hormone synthesis.
- ***Germline mutations*** in the gene ***encoding the TSH receptor*** can cause sporadic or familial nonautoimmune hyperthyroidism.

- ***GD is the most common cause*** of hyperthyroidism in the United States.
- Although ***toxic nodular goiter is less*** common than GD, its prevalence ***increases with age and in the presence of dietary iodine deficiency.***

- Therefore, ***toxic nodular goiter may actually be more common than GD in older patients, especially in regions of iodine deficiency .***

- ***Unlike toxic nodular goiter***, which is ***progressive*** (unless triggered by excessive iodine intake***), remission of mild GD has been reported in up to 30% of patients without treatment .***

- ***Less common causes*** of thyrotoxicosis include the entities of ***painless and subacute thyroiditis***,

- which occur ***due to inflammation of thyroid tissue with release of preformed hormone into the circulation.***

Clinical consequences of thyrotoxicosis

- The ***cellular actions*** of thyroid hormone are ***mediated by T3,*** the active form of thyroid hormone.

- T3 binds to two specific nuclear receptors (thyroid hormone receptoraandb) that regulate the expression of many genes. Nongenomic actions of thyroid hormone include regulation of numerous important physiologic functions.
- ***Thyroid hormone influences almost every tissue and organ system***.
- It increases ***tissue thermogenesis and basal metabolic rate*** and ***reduces serum cholesterol levels and systemic vascular resistance.***

- Some of the most profound effects of increased thyroid hormone levels occur within ***the cardiovascular system***.
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- ***Untreated or partially treated thyrotoxicosis*** is associated with ***weight loss, osteoporosis, atrial fibrillation, embolic events, muscle weakness, tremor, neuropsychiatric symptoms, and rarely cardiovascular collapse and death .***
- ***Only moderate correlation exists between the degree of thyroid hormone elevation and clinical signs and symptoms***.

- Symptoms and signs that result from ***increased adrenergic stimulation*** include ***tachycardia and anxiety*** and may ***be more pronounced in younger patients and those with larger goiters*** .

- The signs and symptoms of mild, or subclinical, thyrotoxicosis are similar to those of overt thyrotoxicosis but differ in magnitude.

- Measurable changes in basal metabolic rate, cardiovascular hemodynamics, and psychiatric and neuropsychological function can be present in mild thyrotoxicosis .

Assessment of disease severity

- Assessment of thyrotoxic manifestations, and especially ***potential cardiovascular and neuromuscular complications***, is essential in formulating an ***appropriate treatment plan.***

- Although it might be anticipated that the ***severity of thyrotoxic symptoms*** is proportional to the ***elevation in the serum levels of free T4and T3***, in one small study of 25 patients with GD, the Hyperthyroid ***Symptom*** Scale did ***not strongly correlate with free T4or T3*** and was inversely ***correlated with age .***

- The importance of age as a determinant of the prevalence and severity of hyperthyroid symptoms has recently been confirmed .
- ***Cardiac evaluation may be necessary, especially in the older patient***, and may require an echocardiogram, electrocardiogram, Holter monitor, or myocardial perfusion studies .
- The need for evaluation should not postpone therapy of the thyrotoxicosis. In addition to the administration ***of b-blockers*** , treatment may be ***needed for concomitant myocardial ischemia, congestive heart failure, or atrial arrhythmias*** .
- ***Anticoagulation*** may be necessary in patients in ***atrial fibrillation*** .

- Goiter size, obstructive symptoms, and the severity of Graves' orbitopathy (GO), the inflammatory disease that develops in the orbit in association with autoimmune thyroid disorders, can be discordant with the degree of hyperthyroidism or hyperthyroid symptoms.

- All patients with known or suspected hyperthyroidism should undergo a comprehensive ***history and physical examination***, including measurement of ***pulse rate, blood pressure, respiratory rate, and body weight***.
- ***Thyroid size, tenderness, symmetry, and nodularity*** should also be assessed along with ***pulmonary, cardiac, and neuromuscular function*** and ***the presence or absence of peripheral edema, eye signs, or pretibial myxedema***

Biochemical evaluation

- ***Serum TSH measurement*** has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected thyrotoxicosis and should be used as ***an initial screening test .***
- However, when thyrotoxicosis is strongly suspected, diagnostic accuracy improves when a serum TSH, free T4, and total T3are assessed at the initial evaluation.
- ***The relationship between free T4and TSH when the pituitary-thyroid axis is intact is an inverse log-linear relationship***; therefore, small changes in free T4result in large changes in serum TSH concentrations.
- ***Serum TSH levels are considerably more sensitive than direct thyroid hormone measurements for assessing thyroid hormone excess .***

- ***In overt hyperthyroidism***, serum ***free T4,T3,or both are elevated, and serum TSH is subnormal*** .
- ***In mild hyperthyroidism***, serum ***T4 and free T4can be normal, only serum T3may be elevated, and serum TSH will be low or undetectable.***
- These laboratory findings have been called "***T3-toxicosis" and may represent the earliest stages of hyperthyroidism caused by GD or an autonomously functioning thyroid nodule***.
- As with T4, total T3 measurements are affected by protein binding. Assays for estimating free T3are less widely validated and less robust than those for free T4. Therefore, ***measurement of total T3 is frequently preferred over free T3 in clinical practice.***

- ***Subclinical hyperthyroidism*** is defined as a ***normal serum free T4 and normal total T3or free T3 , with subnormal serum TSH concentration***.

- Laboratory protocols that store sera and automatically retrieve the sample and add on ***free T4 and total T3 measurements*** when the ***initial screening serum TSH concentrations are low avoid the need for subsequent blood draws***.

- The term "***euthyroid hyperthyroxinemia***" has been used to describe a number of entities, primarily ***thyroid hormone- binding protein disorders***, which cause ***elevatedtotal serum T4 concentrations (and frequently elevated total serum T3 concentrations) in the absence of hyperthyroidism*** .
- These conditions include elevations in T4binding globulin (TBG) or transthyretin ; the presence of an abnormal albumin which binds T4 with high capacity (familial dysalbuminemic hyperthyroxinemia);
- ***TBG excess*** may occur as a hereditary X-linked trait, or it may be acquired as a result of pregnancy or estrogen administration, hepatitis, acute intermittent porphyuria or during treatment with 5-fluorouracil, perphenazine, or some narcotics.

TABLE 3. CAUSES OF THYROTOXICOSIS

Thyrotoxicosis associated with a normal or elevated RAI uptake over the neck[a]
GD
TA or TMNG
Trophoblastic disease
TSH-producing pituitary adenomas
Resistance to thyroid hormone (T_3 receptor β mutation, THRB)[b]
Thyrotoxicosis associated with a near-absent RAI uptake over the neck
Painless (silent) thyroiditis
Amiodarone-induced thyroiditis
Subacute (granulomatous, de Quervain's) thyroiditis
Palpation thyroiditis
Iatrogenic thyrotoxicosis
Factitious ingestion of thyroid hormone
Struma ovarii
Acute thyroiditis
Extensive metastases from follicular thyroid cancer

- In a patient with ***a symmetrically enlarged thyroid***, ***recent onset of orbitopathy,*** and ***moderate to severe hyperthyroidism***, the diagnosis of GD is likely and further evaluation of hyperthyroidism causation is unnecessary.

- ***RAIU measures the percentage of administered RAI that is concentrated into thyroid tissue*** after a fixed interval, usually 24 hours.

- Technetium uptake measurements utilize pertechnetate that is trapped by the thyroid, but not organified.

- Uptake measurements are indicated ***when the diagnosis is in question*** (except during pregnancy and usually during lactation)and distinguishes causes of thyrotoxicosis having elevated or normal uptake over the thyroid gland from those with near-absent uptake .

- ***Uptake is usually elevated*** in patients with ***GD and normal or high in toxic nodular goiter,*** unless there has been a recent exposure to iodine (e.g., radiocontrast).

- The ***RAIU will be near zero*** in patients with ***painless, postpartum, or subacute thyroiditis; factitious ingestion of thyroid hormone; or recent excess iodine intake.***

- Where expertise is available, ***ultrasonography with color flow Doppler can distinguish thyroid hyperactivity (increased flow)*** from destructive thyroiditis .

- This test may be particularly ***useful when radioactive iodine (RAI) is contraindicated, such as during pregnancy or breastfeeding***.

- The ***ratio of total T3to total T4 can also be useful*** in assessing the etiology of thyrotoxicosis when scintigraphy is contraindicated.

- Because a ***hyperactive gland produces more T3 than T4,T3*** will be elevated above the upper limit of normal more than T4 in thyrotoxicosis caused by hyperthyroidism, ***whereas T4is elevated more than T3in thyrotoxicosis caused by thyroiditis*** ; in one study the ratio of total T3to total T4 (ng/lg) was>20 in GD and toxic nodular goiter, and<20 in painless or postpartum thyroiditis.

- ***A high T4to T3ratio may be seen in thyrotoxicosis factitia*** (from exogenous levothyroxine).

treatment hyperthyroidy

- ***RAI therapy***:
- ***Women planning a pregnancy in the future (in more than 6 months*** following RAI administration, provided thyroid hormone levels are normal), individuals with comorbidities increasing surgical risk, and patients with previously operated or externally irradiated necks, or lack of access to a high-volume thyroid surgeon, and patients with ***contraindications to ATD useor failure*** to achieve euthyroidism during treatment with ATDs.

- Patients with ***periodic thyrotoxic hypokalemic paralysis***, ***right heart failure pulmonary hypertension***, or ***congestive heart failure*** should also be considered good candidates for RAI therapy.

- ***ATDs***:
- Patients with high likelihood of remission (patients, especially ***women***, with ***mild disease***, ***small goiters***, and ***negative or low-titer TRAb***); ***pregnancy;*** the ***elderly or others with comorbidities increasing surgical risk*** or with ***limited life expectancy***; individuals in nursing homes or other care facilities who may have limited longevity and are unable to follow radiation safety regulations; patients with ***previously operated or irradiated necks***; patients with ***lack of access to a high-volume thyroid surgeon***; patients with moderate to severe active GO; and patients who need more rapid biochemical l disease control.

- Surgery:
- Women ***planning a pregnancy in<6 months*** provided thyroid hormone levels are normal (i.e., possibly before thyroid hormone levels would be normal if RAI were chosen as therapy); ***symptomatic compression or large goiters*** (‡80 g); ***relatively low uptake of RAI***; when ***thyroid malignancy is documented or suspected*** (e.g., suspicious or indeterminate cytology); ***large thyroid nodules*** especially if greater than 4 cm or if nonfunctioning, or hypofunctioning on 123 Ior 99m Tc pertechnetate scanning; ***coexisting hyperparathyroidism requiring surgery***; especially if TRAb levels ar particularly high; and ***patients with moderate to severe active GO.***

- ***Prior to initiating ATD therapy for GD***, we suggest that patients have a ***baseline complete blood count***, including white blood cell (WBC) count with differential, and ***a liver profile including bilirubin and transaminases***.

- ***At the start of MMI therapy***, ***initial doses of 10- 30 mg daily*** are used to restore euthyroidism, and the dose can then be titrated down to a maintenance level (generally 5- 10 mg daily) .
- The dose of ***MMI should be targeted to the degree of thyroid dysfunction*** because too low a dose will not restore a euthyroid state in patients with severe disease and an excessive dose can cause iatrogenic hypothyroidism in patients with mild disease .
- In addition, adverse drug reactions are more frequent with higher MMI doses. Thus, it is important to use an MMI dose that will achieve the clinical goal of normalization of thyroid function reasonably rapidly, while minimizing adverse drug effects.

- The task force suggests the following as a rough guide to initial MMI daily dosing: 5–10 mg if free T4is 1–1.5 times the upper limit of normal; 10–20 mg for free T41.5–2 times the upper limit of normal; and 30–40 mg for free T42–3 times the upper limit of normal.

- These rough guidelines should be tailored to the individual patient, incorporating additional information on symptoms, gland size, and total T3 levels where relevant.
- ***Serum T3 levels are important to monitor initially because some patients normalize their free T4levels with MMI but have persistently elevated serum T3, indicating continuing thyrotoxicosis .***

- MMI has the benefit of once-a-day administration and a reduced risk of major side effects compared to PTU.
- ***PTU has a shorter duration of action and is usually administered two or three times daily,*** starting with 50–150 mg three times daily, depending on the severity of the hyperthyroidism.
- As the clinical findings and thyroid function tests return to normal, reduction to a maintenance PTU dose of 50 mg two or three times daily is usually possible.
- When more rapid biochemical control is needed in patients with severe thyrotoxicosis, an initial split dose of MMI (e.g., 15 or 20 mg twice a day) may be more effective than a single daily dose because the ***duration of action of MMI may be less than 24 hours*** .

- ***Higher doses of antithyroid medication*** are sometimes administered continuously and ***combined with L-thyroxine in doses to maintain euthyroid levels*** (***so-called block and replace therapy***).

- However, this ***approach is not generally recommended*** because it has been shown to result in a higher rate of ATD side effects .

Adverse effects of ATDs

- adverse effects of ATDs can be divided into common, ***minor allergic side effects*** and rare but serious ***allergic/toxic events such as agranulocytosis, vasculitis, or hepatic damage.***

- ***ATD-associated agranulocytosis is uncommon, it is life-threatening. PTU at any dose appears to be more likely to cause agranulocytosis compared with low doses of MMI .***

- ***MMI hepatotoxicity has been described as typically cholestatic, but hepatocellular disease may be seen . In contrast, PTU can cause fulminant hepatic necrosis that may be fatal; liver transplantation has been necessary in some patients taking PTU .***

- ***PTU and rarely MMI*** can cause antineutrophil cytoplasmic antibody ***(pANCA)-positive small vessel vasculitis*** as well as drug-induced lupus .

- The risk appears to ***increase with duration of therapy*** as opposed to other adverse effects seen with ATDs that typically occur early in the course of treatment .

- In most cases, the ***vasculitis resolves with drug discontinuation,*** although ***immunosuppressive therapy may be necessary*** .

- An assessment of ***serum free T4 and total T3*** should be obtained ***about 2-6 weeks after initiation of therapy***, depending on the severity of the thyrotoxicosis, and the dose of medication should be adjusted accordingly.

- ***Serum T3should be monitored*** because the serum free T4 levels may normalize despite persistent elevation of serum total T3 .

- ***Serum TSH may remain suppressed for several months after starting therapy,*** and it is therefore not a good parameter for monitoring therapy early in the course.

- Once the patient is euthyroid, the dose of MMI can usually be decreased by 30%–50%, and biochemical testing repeated in 4–6 weeks.

- Once euthyroid levels are achieved with the minimal dose of medication, clinical and laboratory evaluation can be undertaken at intervals of 2–3 months.

- If a patient is receiving long-term MMI (>18 months), this interval can be increased to 6 months .

- A ***differential WBC count*** should be obtained ***during febrile illness*** and at the ***onset of pharyngitis in*** all patients taking antithyroid medication.

- There is ***insufficient evidence*** to recommend for or ***against routine monitoring of WBC counts in patients taking ATDs.***

- ***Liver function and hepatocellular integrity*** should be assessed in patients taking MMI or PTU who experience ***pruritic rash, jaundice, light-colored stool or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea, or fatigue***.

- There is insufficient information to recommend for or against routine ***monitoring of liver function tests in patients taking ATDs***.

- ***Minor cutaneous reactions*** may be managed with concurrent ***antihistamine therapy without stopping the ATD.***
- ***Persistent symptomatic minor side effects*** of antithyroid medication should be managed by ***cessation of the medication and changing to RAI or surgery, or switching to the other ATD when RAI or surgery are not options.***
- In the case of a serious allergic reaction, prescribing the alternative drug is not recommended.

- If MMI is chosen as the ***primary therapy for GD***, the medication should be continued for ***approximately 12-18 months***, then discontinued if the TSH and TRAb levels are normal at that time.

- If a patient with ***GD becomes hyperthyroid after completing a course of MMI,*** consideration should be given to ***treatment with RAI or thyroidectomy.***

- Continued low-dose MMI treatment for longer than 12–18 months may be considered in patients not in remission who prefer this approach.

Table 10. Subclinical Hyperthyroidism: When to Treat

Factor	*TSH (<0.1 mU/L)*	*TSH (0.1–0.4 mU/L)*[a]
Age >65 years	Yes	Consider treating
Age <65 years with comorbidities		
Heart disease	Yes	Consider treating
Osteoporosis	Yes	Consider treating
Menopausal, not on estrogens or bisphosphonates	Yes	Consider treating
Hyperthyroid symptoms	Yes	Consider treating
Age <65 years, asymptomatic	Consider treating	Observe

- When TSH is ***persistently<0.1 mU/L***, treatment of SH is recommended in ***all individuals ‡65 years of age;*** in patients with ***cardiac risk factors, heart disease or osteoporosis; in postmenopausal women who are not on estrogens or bisphosphonates; and in individuals with hyperthyroid symptoms .***

- ***How should thyrotoxicosis due to destructive thyroiditis be managed?***

- ***Several varieties of thyroiditis*** can present with temporary thyrotoxicosis as part of a ***classic triphasic course*** (***thyrotoxicosis, hypothyroidism, recovery***), including subacute thyroiditis, painless (silent) thyroiditis, acute (suppurative) thyroiditis, palpation (traumatic) thyroiditis, postpartum thyroiditis, and drug-induced thyroiditis.

- In general, thyroid dysfunction caused by thyroiditis is ***less severe*** than that seen with other forms of endogenous thyrotoxicosis ; ***RAIU is universally low*** during the thyrotoxic stage, owing to leaking of preformed thyroid hormone with ***suppression of serum TSH concentrations***.

Subacute thyroiditis

- Subacute thyroiditis, also called subacute granulomatous or de Quervain thyroiditis, is a common cause of thyroid pain . The ***diagnosis*** of subacute thyroiditis is ***based on clinical history, physical examination, laboratory data, and RAIU.***
- Subacute thyroiditis presents with ***moderate-to-severe pain in the thyroid***, often ***radiating to the ears, jaw, or throat***.
- The pain may begin focally and spread from one side to the other of the gland over several weeks. Patients may have a ***prodrome of malaise, low-grade fever, pharyngitis symptoms, and fatigue***.
- The thyroid may be slightly enlarged and is firm and painful to palpation. Subacute thyroiditis is thought to be due to a ***sequela of an upper respiratory viral infection that involves the thyroid gland.***

- early in the course of the disease, patients may ***have clinical findings of thyrotoxicosis, although this is often mild***.
- The serum TSH level is suppressed, and the ***free T4level may be elevated preferentially compared to the total T3 level***, in contrast to other endogenous forms of thyrotoxicosis, although substantial overlap occurs among the etiologies .
- In addition to laboratory evidence of thyrotoxicosis, the ***erythrocyte sedimentation rate (ESR) or Creactive protein is elevated, and mild anemia and elevation of the WBC count are common.***
- Up to 25% of patients have low concentrations of antithyroid antibodies .

- ***Thyroid ultrasonography*** shows ***diffuse heterogeneity, focal hypoechoic areas, and decreased or normal color flow Doppler,*** rather than the enhanced flow characteristic of GD .

- A biopsy of the thyroid gland is usually not necessary in subacute thyroiditis. However, if a biopsy is performed due to uncertainty of the diagnosis, its result shows ***granulomatous infiltrate and giant cells, consistent with a viral infection .***

- The ***thyrotoxic phase usually lasts 3-6 weeks,*** ending when the thyroid stores of preformed hormone are depleted.
- About 30% of patients subsequently enter a ***hypothyroid phase that can last up to 6 months.***
- Thyroid pain and the elevated ESR have usually resolved by this time, and the predominant clinical features are those of hypothyroidism with a small nontender goiter.
- Most patients ***become euthyroid again within 12 months of disease onset***, although ***5%-15% have persistent hypothyroidism*** .
- In addition, ***recurrence rates of 1%-4% have been reported .***

- Patients with ***mild symptomatic subacute thyroiditis*** should be treated initially ***with b-adrenergic-blocking drugs*** and nonsteroidal anti-inflammatory agents ***(NSAIDs)***.
- ***Corticosteroids*** should be used ***instead of NSAIDs when patients fail to respond*** or present ***initially with moderate to severe pain and/or thyrotoxic symptoms***.

- ***With NSAIDs, the median time for resolution of pain is 5 weeks (range 1-20 weeks) . Patients who fail to respond to full doses of NSAIDs over several days should be treated instead with corticosteroid therapy.***

- Standard recommendations are to use ***prednisone 40 mg daily for 1-2 weeks followed by a gradual taper over 2-4 weeks or longer***, depending upon clinical response.

- A retrospective review found that patients treated with ***corticosteroids*** at similar doses had ***more rapid resolution of pain*** (mean duration, 8 days) compared with those treated with NSAIDs (mean duration, 35 days).

- However, symptoms can ***recur as the dose of corticosteroid is reduced*** .
- A more recent study reported that a ***lower initial daily dose of 15 mg of prednisolone, with tapering by 5 mg every 2 weeks, was effective.***

- ***Levothyroxine*** may be employed during the hypothyroid stage but should be ***withdrawn after 3-6 months***, with recovery of normal function verified by thyroid function testing.

- ***ATDs have no role in the treatment of subacute thyroiditis.***

- ***Painless or silent thyroiditis*** classically presents with the same ***triphasic course described for subacute thyroiditis***, but ***with no prodrome, neck pain, or elevated ESR, WBC count, or C-reactive protein*** .
- The ***postpartum period is the most common time*** when painless thyroiditis is seen, but painless thyroiditis can ***also occur in nonpregnant women and in men***.

- Painless thyroiditis has been described in some types of ***drug-induced thyroid dysfunction***, including that associated with ***lithium or cytokine therapy. Postpartum and druginduced thyroiditis***.
- A small nontender goiter is common in all types of painless thyroiditis.

- The ***thyrotoxic phase*** occurs in 5%–20% of patients and typically ***lasts 3–4 months***.

- The ***hypothyroid phase*** is more common or at least is recognized more often, ***lasting up to 6 months***.

- ***Normal thyroid function*** is reestablished by ***12 months in most patients***, but ***10%–20% have persistent hypothyroidism.***

Table 17. Unusual Causes of Thyrotoxicosis

Disorder	*Diagnosis*	*Primary management*
TSH-producing adenoma	Pituitary MRI, α-subunit to TSH ratio	Surgical removal
Struma ovarii	RAI uptake over pelvis	Surgical removal
Choriocarcinoma	hCG elevation in the absence of pregnancy	Surgical removal
Thyrotoxicosis factitia (surreptitious LT_4 or LT_3)	Absence of goiter; suppressed thyroglobulin	Psychosocial evaluation
Functional thyroid cancer metastases	Whole-body RAI scanning	RAI ablation, embolization and/or surgical removal


Thank You!