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Q: How do I manage my patients with thyrotoxicosis until they see the endocrinologist?

A nonpregnant adult patient presented with progressive anxiety, heat intolerance, and palpitations. Thyroid-stimulating hormone was suppressed at less than 0.01 mIU/mL (reference range 0.5–4.0). Repeat testing showed thyroid-stimulating hormone again at less than 0.01 mIU/mL, with free thyroxine (T4) about 2 times the upper limit of normal at 2.98 ng/dL (0.8–1.8). I diagnosed the patient with thyrotoxicosis and placed a referral to endocrinology, but the patient will not be seen for about 8 weeks and is worried about progressively feeling worse. What steps can be taken in the meantime?

A: For a patient with symptomatic thyrotoxicosis, the first step is a referral to endocrinology, but there can be a long wait time. In the interim, a primary care physician can initiate beta-blockers promptly for symptomatic relief, obtain radioactive iodine uptake and scan if true hyperthyroidism is suspected, and, if high uptake is noted, start an antithyroid drug.

■ TOO FEW ENDOCRINOLOGISTS

Symptomatic hyperthyroidism is a common problem, affecting approximately 1% of the population.¹ Many primary care physicians would promptly and appropriately refer their patient with thyrotoxicosis to an endocrinologist. However, in an era of widespread and worsening physician shortages, endocrinologists are in short supply and high demand.² Wait times of several weeks to even months are common. Meanwhile, the patient is symptomatic. But the primary care physician can do a lot, both diagnostically and therapeutically, until care is established with the endocrinologist.

■ STEPS THAT CAN BE TAKEN WHILE AWAITING ENDOCRINOLOGY REFERRAL

1. Determine whether the patient has true hyperthyroidism or excess thyroid hormone due to another cause

This distinction is important, as true hyperthyroidism, ie, increased endogenous thyroid hormone production, is unlikely to resolve spontaneously and should respond to thyroid-directed therapy like thionamides (methimazole and propylthiouracil), radioactive iodine ablation, or thyroidectomy. However, thyroid-directed therapy is unnecessary, ineffective, and potentially harmful for other forms of thyrotoxicosis such as thyroiditis (in which preformed thyroid hormone is released from an inflamed thyroid) or exogenous sources of thyroid hormone.

Exogenous thyrotoxicosis may not require specific testing. This is most obvious when the patient is known to be taking levothyroxine or other thyroid hormone preparations. Surreptitious or accidental exposure, often from weight loss or other health supplements, requires a higher index of suspicion.³ Patients should be queried about all nonprescription supplements. The main treatment for exogenous thyrotoxicosis is to reduce or eliminate the source of thyroid hormone.

For all remaining patients, the most informative approach is to distinguish true hyperthyroidism (high uptake in the thyroid) from other forms of thyrotoxicosis (low uptake in the thyroid). The gold standard test is really 2 tests in 1: a radioactive iodine uptake study and scan. The “uptake” portion measures the percentage of administered iodine 123 that is present in the thyroid, typically 24 hours after administration. Accompanying nuclear medicine scintigraphy, or gamma scan, images

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taken at the 24-hour mark can allow the clinician to visually differentiate between high-uptake states such as Graves disease (diffuse, symmetric uptake), single autonomous nodule (large single focus of concentrated iodine 123), or autonomous multinodular gland (patchy and scattered uptake throughout the thyroid).

Technetium 99m pertechnetate scintigraphy, which measures technetium trapped in the thyroid at approximately 20 minutes, is a quicker test that can be considered if the clinical situation (eg, the thyroid physical examination or prior thyroid imaging) suggests a single toxic adenoma or toxic multinodular goiter.⁴

These tests are ordered through radiology or nuclear medicine.

Importantly, symptomatic treatment (see step 2 below) can be started before radiotracer testing is performed. Thyroid-specific treatment (see step 3 below) should be deferred until after radiotracer testing is done to avoid skewing results. An additional pitfall of using radiotracers is that patients with a significant iodine exposure, such as iodinated contrast in the past several weeks or amiodarone use in the past several months, will have falsely low uptake of either iodine 123 or technetium. Finally, breastfeeding and especially pregnancy are contraindications to radiotracers.⁵

A classic presentation of Graves disease, the most common cause of endogenous hyperthyroidism, can be diagnosed without imaging. With symmetric goiter, recent-onset orbitopathy, and moderate or severe hyperthyroidism, other etiologies of thyrotoxicosis are unlikely. The diagnosis can be confirmed with elevated serum levels of thyroid-stimulating immunoglobulins.⁴

2. Provide symptomatic relief for all forms of thyrotoxicosis

Outpatients with adrenergic symptoms of thyrotoxicosis, such as palpitations, tremors, and anxiety, often desire prompt relief. Oral beta-blockers, such as propranolol or atenolol, can be prescribed without affecting subsequent testing. The usual considerations apply—for example, patients at risk of bronchospasm, such as those with asthma, present a relative contraindication to the use of beta-blockers.¹ Attention must also be paid to pretreatment and posttreatment heart rates and blood pressures, as beta-blockers can lower both.

Propranolol may be desirable compared with other beta-blockers, as it alone has been demonstrated to decrease peripheral conversion of T4 to triiodothyronine (T3), at least at high doses (hundreds of milligrams per day).⁶ In the outpatient setting, propranolol can be prescribed at doses of 10 to 40 mg, 3 or 4 times daily.

Alternatively, a more cardioselective beta-blocker such as atenolol (25–100 mg 1 or 2 times daily) or metoprolol tartrate (25–50 mg 2 or 3 times daily) can be used.⁴

Beta-blocker therapy alone will usually suffice for self-limited causes of thyrotoxicosis such as thyroiditis (including postpartum thyroiditis) or exogenous thyroid hormone (with concomitant reduction or elimination of this exposure).

3. Initiate antithyroid medication for true hyperthyroidism

For patients with true hyperthyroidism awaiting consultation with endocrinology, it is very reasonable to consider oral thionamides such as methimazole or propylthiouracil. These medications directly inhibit thyroid hormone synthesis.⁷ This means they will affect thyroid function tests such as thyroid-stimulating hormone and free or total T4 and T3, as well as thyroid uptake and scintigraphy. Hence, as mentioned, ideally they are not initiated until after all diagnostic testing is complete.

Methimazole is typically preferred over propylthiouracil for treatment of nonpregnant adult outpatients because it is dosed less frequently and because of greater concerns for liver toxicity with propylthiouracil.¹ The starting dose depends on the degree of severity of thyrotoxicosis, as determined by both clinical signs and symptoms and biochemical values from laboratory testing. Many guidelines and review articles advocate for basing starting doses on free T4 values^{1,4,7}:

- If free T4 levels are 1 to 1.5 times the upper limit of normal: methimazole 5 to 10 mg once daily
- If free T4 levels are 1.5 to 2 times the upper limit of normal: methimazole 10 to 20 mg once daily
- If free T4 levels are greater than or equal to 2 to 3 times the upper limit of normal: methimazole 20 to 40 mg daily in divided doses (eg, 10–20 mg twice daily).

After methimazole is started, thyroid function tests (especially free T4 and either free or total T3) should be repeated every 2 to 6 weeks until euthyroidism is achieved, then every 8 to 12 weeks thereafter, pending endocrinology consultation.^{4,7} Assessment of T3 in addition to T4 is necessary, as free T4 may normalize despite persistent T3 toxicosis.⁴ Methimazole can be titrated down as thyrotoxicosis improves.⁷ Note that thyroid-stimulating hormone may remain suppressed for several months after starting thionamides, so the T4 and T3 assessment is more helpful in the early phase of treatment.

Thionamides can rarely cause hepatotoxicity as well as agranulocytosis or other cytopenias. Rash, affecting

TABLE 1
Recommended initial approach to thyrotoxicosis

Management area	Recommended plan
Diagnostic tests	Thyroid-stimulating hormone, free thyroxine (T4), free or total triiodothyronine (T3), thyroid-stimulating immunoglobulins, radioactive iodine uptake and scan
Symptomatic treatment of all patients (will not affect diagnostic tests)	Propranolol 10–40 mg 3 or 4 times daily <i>or</i> Atenolol 25–100 mg 1 or 2 times daily <i>or</i> Metoprolol tartrate 25–50 mg 2 or 3 times daily
Thyroid-directed treatment—if any 1 of elevated thyroid-stimulating immunoglobulins <i>or</i> high uptake of iodine 123 <i>or</i> high uptake of technetium 99m pertechnetate (will affect diagnostic tests) is found	Methimazole dosing based on free T4 levels: 1–1.5 × upper limit: 5–10 mg daily 1.5–2 × upper limit: 10–20 mg daily 2–3 × upper limit: 10–20 mg twice daily

Based on information from references 1,4,6.

6% of treated patients, is the most frequently reported side effect with methimazole.⁷ Patients starting methimazole should have a baseline complete blood cell count and liver biochemistry testing to identify any preexisting abnormalities. Methimazole and propylthiouracil should be avoided in patients with a baseline absolute neutrophil count less than $1.0 \times 10^9/L$ (reference range $1.8\text{--}7.7 \times 10^9/L$) or transaminase levels exceeding 5 times the upper limit of normal.⁴

Serial complete blood cell count and liver biochemistry testing are not necessary, but symptom-driven laboratory testing is recommended.⁴ For example, white blood cell count with differential should be measured for any febrile illness or acute pharyngitis, while liver biochemistries should be measured for jaundice, light-colored stool or dark urine, nausea, or new pruritic rash.

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THE BOTTOM LINE

Thyrotoxicosis is commonly encountered in primary care. Ideally, a patient diagnosed with thyrotoxicosis will be managed symptomatically with beta-blockers, and then will promptly (perhaps within 2–4 weeks) consult with an endocrinologist for more detailed diagnosis and management. But if the known or suspected wait time for endocrinology consultation is much longer, the astute primary care physician can start beta-blockers promptly for symptomatic relief, obtain radioactive iodine uptake and scan, and, if high uptake is noted, start methimazole.

See Table 1 for a summarized approach.^{1,4,6}

DISCLOSURES

The author reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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