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Objectives

In India the prevalence of hyperthyroidism ranges from 0.9% to 1.5%. Suboptimal diagnosis and management in patients with hyperthyroidism may lead to complications which may be life-threatening. There is a need for a comprehensive clinical practice recommendations to optimize patient care and improve patient outcomes.

Methods

The Indian Thyroid Society (ITS) clinical practice recommendations have been formulated based on consultation with expert endocrinologists of India after examination of relevant evidence using a systematic literature search approach.

Results

The ITS clinical practice recommendations include 4 distinct sections: (1) Introduction; (2) Diagnosis; (3) Management of Hyperthyroidism which includes the role of beta-blockers, management of Graves' disease, multinodular goiter, toxic adenoma (4) Sections on thyroiditis, thyroid storm and hyperthyroidism in women with considerations to pregnancy and lactations have also been included

Conclusion

Evidence based recommendations have been developed to optimize treatment in patients with hyperthyroidism with emphasis on diagnosis and optimizing treatment. Accurate diagnosis is a precedent to etiology-based management protocols for the achievement of euthyroidism while minimizing complications. Anti-thyroid drugs are the first line treatment in Graves' hyperthyroidism management. One notable new theme is the maintenance treatment of Graves' disease patients on the lowest possible dose to maintain euthyroidism for long duration (5 years). Multinodular goiter and toxic adenoma also require control of thyrotoxicosis with antithyroid drugs in the initial phase. Long term antithyroid drugs are now considered in multinodular goiter in patients not suitable for radioactive iodine or surgery. Management of special cases of hyperthyroidism including amiodarone induced thyroiditis, hyperthyroidism in pregnancy and thyroid storm have been discussed. The recommendations provide guidance in the management of patients with hyperthyroidism to facilitate clinical decision making of health care professionals in the management of patients with hyperthyroidism.

Hyperthyroidism Overview in Adults

Contents

1.Introduction

Thyroid hormones influence the metabolism, growth, and functioning of all major organ systems. Thyroid hormones include thyroxine (T4) and triiodothyronine (T3), which are secreted in a 20:1 ratio, respectively. T4 is transformed into active T3, which has three to four times the potency of T4.[i]

Hyperthyroidism is a state of thyrotoxicosis due to intrinsic thyroid gland hyperfunction leading to increased synthesis and high circulating thyroid hormone. Thyrotoxicosis is the clinical state as a result of increased thyroid hormones in the body originating from any cause. [i]

Based on laboratory results, hyperthyroidism is classified as either subclinical or overt. Reduced serum TSH levels and increased levels of free serum triiodothyronine (T3) and/or free thyroxine (T4) indicate overt hyperthyroidism. Reduced serum TSH levels and normal serum levels of free T3 and free T4 indicate subclinical hyperthyroidism.[i]

If uncontrolled, hyperthyroidism can result in osteoporosis, congestive heart failure, atrial fibrillation, embolic events, tremors, weakness, and neuropsychiatric symptoms. It can also have a negative impact on pregnancy outcomes and raise death rates.[ii]

1.1 Prevalence

Globally, 0.2-1.3% of the population suffers from hyperthyroidism. In the United States, the prevalence of hyperthyroidism is approximately 1.2% (0.5% overt and 0.7% subclinical).[iii]

In India the prevalence of hyperthyroidism ranges from 0.9% to 1.5% in people living in community (not seeking medical attention). In patients attending hospital for care of thyroid disorders, the prevalence ranges from 1.79% to 5.3%.

Table 1: Prevalence of Overt Hyperthyroidism in India

Patient Population	*Screening Studies in communities.*					*Studies in Hospitals*		
Indian Study:	Unnikrishnan et al.[iv]	Marwaha et al.[v]	Ganie et al.[vi]	Abraham et al.[vii]	Velayutham et al.[viii]	Bose et al.[ix]	Nirmalanandan et al[x]	Sahu et al[xi]
State	Cochin	Delhi	Jammu & Kashmir	Puducherry	Tamil Nadu	Madhya Pradesh	Kerala	Odisha
Prevalence	**1.3%**	**1.1%**	**0.9 %**	**1.2%**	**1.5%**	**1.79%**	**2.5%**	**5.3%**
Patient population	(population-based study on 971 adult subjects)	(4409 adult members of resident welfare associations of 5 residential colonies)	(768 individuals from 5 districts of Jammu and Kashmir	(505 women who attended a Health Clinic)	(1292 female college students in seven colleges in Madurai District)	(28,677 patients who were turned out to hospital for thyroid hormone profile tests)	(2401 admitted in the general ward with thyroid disorders)	(9649 requisition forms for TFTs, from patients in a tertiary care center)

1.2 Etiopathogenetic Causes of Thyrotoxicosis[xii]

Excessive TSH receptor stimulation is seen in Graves' hyperthyroidism, hCG-related thyrotoxicosis, and TSH adenoma. hCG-related thyrotoxicosis includes gestational transient thyrotoxicosis, familial gestational hyperthyroidism, hydatiform mole and choriocarcinoma.

Autonomous thyroid hormone secretion is seen in Toxic multinodular goiter and Solitary toxic adenoma, in which thyroid gland nodules secrete excess hormones, independent from TSH or TSH

receptor antibodies. Autonomous hormone overproduction can also result from familial or sporadic non-autoimmune hyperthyroidism, which is caused by genetic or environmental causes.

Destructive thyroiditis encompasses subacute de Quervain and silent thyroiditis, post-partum thyroiditis, acute suppurative thyroiditis and Drug-induced thyroiditis. Drug-induced forms include iodide-induced thyrotoxicosis, amiodarone, cytokine, tyrosine-kinase inhibitors, and immune checkpoint inhibitors.

Extrathyroidal sources of thyroid hormone include thyrotoxicosis factitia and hamburger thyrotoxicosis, alongside rare occurrences like struma ovarii and metastases of differentiated thyroid cancer.

Out of these, there are four major causes of thyrotoxicosis which are Graves' disease, Multinodular goiter, Toxic adenoma and thyroiditis.[xii]

1. **Graves' disease:**

Graves' disease (GD) is the most common cause of hyperthyroidism in iodine-sufficient geographic locations. Graves' disease is a type of autoimmune disease characterized by presence of Thyrotropin Receptor Antibodies (TRAb) also known as Thyroid stimulating hormone receptor (TSHR) autoantibodies which activate TSH receptors, resulting in excessive thyroid hormone synthesis. Hyperthyroidism is more common in women. Approximately 30% of hyperthyroidism patients have family members who have GD or Hashimoto's thyroiditis. Environmental factors such as smoking, increased iodine intake, stress, and pregnancy can all contribute to hyperthyroidism.[xii] Thyroid ophthalmopathy/orbitopathy, pretibial myxedema (localized fluid-filled and thickened pretibial plaque formation), thyroid acropachy (clubbing of the fingers and toes accompanied by soft-tissue swelling of hands and feet, and periosteal bone growth formation), may be seen in a case of Graves' disease.[xiii] Diamond's triad in Graves' disease refers to a rare combination of exophthalmos, pretibial myxedema, and thyroid acropachy.

2. **Toxic multinodular goiter (Plummer Disease)**

A normal thyroid gland usually has a homogenous structure. Follicular cells that are genetically heterogenous as well as acquisition of inheritable qualities in the mother cells lead to loss of

anatomical and functional integrity of the follicles. These factors when acted on by the elevated TSH as well as external events such as iodine deficiency, goitrogens, inborn errors of thyroid hormone synthesis and local growth regulating factors of the tissues lead to proliferation of the follicle. Growth and fusion of the follicles, which are the structural and functional units of the thyroid glands, may lead to formation of nodules. A long-standing formation of diffuse and nodular follicles may be detected as a mass in the neck, presenting as goiter.[xiv]

In geographical areas of iodine deficiency there is higher prevalence of multinodular goiter (MNG). It is hypothesized that in iodine deficient states the thyroid gland goes through hyperplasia, which is an effect of increased TSH stimulation. When there is iodide repletion or a decreased demand for thyroid hormones, there is an increase in the colloid storage and the thyroid gland enters a resting phase. When cycles of iodine deficiency followed by iodine repletion or decreased demand of thyroid hormones occur, this may result in formation of the multinodular goiter. After several decades of MNG, a large proportion of patients develop hyperthyroidism.[xiv]

Iodine deficiency became a recognized national public health concern in India as early as the 1960s. In 1962, the Indian government established the National Goiter Control Programme (NGCP) to identify goiter-endemic zones in the country and supplement the iodine intake of the entire population in these areas. The expansion of NGCP resulted in the determination that all edible salts in India were to be iodized by 1992. [xv]

Toxic multinodular goiter is more common in older adults (aged >50 years) compared to GD. Unlike GD, toxic nodular goiter is progressive (except in cases triggered by excessive iodine intake). [xvi]

3. Toxic Adenoma

Adenomas in the thyroid gland are non-cancerous tissue growths which could be dormant or active. Active adenomas which produce excessive thyroid hormones are known as toxic thyroid adenomas. [xvii] Toxic adenoma is caused due to somatic activating mutations of genes regulating the growth and thyroid hormone synthesis. It is a single hyper-functioning nodule in the thyroid gland, results in localized excess thyroid hormone production. It is characterized by weight loss, palpitations, and heat sensitivity and is commonly found in patients aged 30-60 years.[xii]

4. Thyroiditis

Thyroiditis is characterized by inflammation of the thyroid tissue, which causes preformed hormones to be released into the bloodstream. Medications, particularly amiodarone, can cause painless thyroiditis. Sub-acute thyroiditis, which is generally viral in origin, induces thyroid inflammation as well as pain and fever.[xii]

Indian Evidence: Prevalence of Hyperthyroidism in India

In 2022, a cross-sectional study was conducted by Nijith and Ranjan in South India including newly diagnosed patients with hyperthyroidism. 140 patients were recruited, out of which 85% were females. Majority patients had less than one year duration for symptoms. Graves' disease was present in 59.3% patients and multinodular goiter was seen in 36.4%.[xviii]

In another study in central Kerala by Philip et al, patients who had routine health checkups, surgical fitness or pregnant patients who had an incidental finding of biochemical thyrotoxicosis were included for analysis. Patients in whom symptoms of thyroxicosis were present or who were under clinical suspicion of thyrotoxicosis were excluded. 57 patients were included with an average age of 32.8 years and a female:male ratio of 3.3:1. In these patients thyroid ultrasound and thyroid scan were undertaken. 91% (n=52) patients had subacute thyroiditis; 47 patients became euthyroid and 5 became subclinical hypothyroid in 3 months. Graves' disease was detected in 9% patients. Authors emphasized that in patients with thyroiditis, it is important to take the wait and watch approach instead of starting with antithyroid drugs especially if uptake scans are inaccessible. [xix]

2. Diagnosis

2.1 Clinical Diagnosis

One of the primary obstacles to the successful treatment of thyroid dysfunction arises from the risk of under recognition or misinterpretation of these conditions, leading to frequent instances of misdiagnosis. Hyperthyroidism, in particular, presents a challenge as its diagnosis may be delayed

or missed, primarily because its symptoms can manifest across various organ systems, making it easily confounded with other conditions. [xx, xxi]

Table 2: Signs and Symptoms of Hyperthyroidism [xii,xviii]

System	Symptoms	Signs
General	Weight loss	Increased sweating
	Fatigue	Hoarseness of voice
	Weakness esp. in elderly	
	Heat intolerance	
	Increased appetite	
Cardiovascular	Palpitations	Tachycardia with/without irregular rhythm
	Ankle edema	Atrial fibrillation
		Wide pulse pressure
		Systolic Hypertension
		Heart failure
Neuropsychiatry	Restlessness, Anxiety	Brisk tendon reflexes
	Sleep disturbances	Finger or tongue tremor
	Depression	Muscle wasting
	Poor concentration	
	Tremors	
	Muscle weakness	
	Periodic Paralysis	
Reproductive	Oligomenorrhea,	Subfertility in women
	Irregular menstrual cycles	
	Impaired libido in men	
Gastrointestinal	Loose stools, diarrhea, nausea	Increase in frequency of bowel movements
Musculoskeletal	Fragility fractures	Unexplained osteoporosis
Endocrinology	Goiter	Gynaecomastia
		Pretibial myxoedema
Ophthalmology	Bulging eyes	Upper lid retraction

	Stare	
Dermatology		Plummer's nail
		Warm moist skin

Symptoms of hyperthyroidism may also include urinary symptoms manifesting, after one to six months after onset of other symptoms, as voiding abnormalities. Reduced flow rates, increased post-void residual volume, enlarged bladder capacity and increased perineal muscle electromyographic activity was noted in Goswami et al. These abnormalities were controlled after return to euthyroidism with carbimazole therapy.[xxii]

Neuropsychiatric manifestations in the form of anxiety, dysphoria, emotional lability, mania, psychosis, or a mix of mania and psychosis are also common in hyperthyroidism.[xxiii, xxiv]

In an Indian study by Goyal et al (2021), thyroid function testing in 40 patients presenting with the first episode of mania revealed that 7.5% had hyperthyroidism and 5% had subclinical hyperthyroidism.[xxv]

Individuals with suspected or confirmed hyperthyroidism require a thorough evaluation, including a detailed medical history and comprehensive physical examination. Vital signs such as pulse rate, blood pressure, respiratory rate, and body weight should be assessed. Examination of the thyroid gland for size, tenderness, symmetry, and nodularity is important, along with evaluating pulmonary, cardiac, and neuromuscular function. Additionally, the presence or absence of peripheral oedema, eye signs, or pretibial myxedema should be noted.[xvi,xii]

Apathetic hyperthyroidism is a departure from the hyperkinetic clinical presentation of classical hyperthyroidism in that it is characterized by weakness, weight loss, lethargy, depression and arrythmia. Since this presentation of hyperthyroidism is commonly seen in the middle aged and the elderly, the associated signs and symptoms may be mistaken as the natural process of aging. Wu et al. 2010 determined that decreased FT3/FT4 ratio, increased alanine aminotransferase (ALT) levels and bone-specific alkaline phosphatase (BAP) levels were associated with apathetic hyperthyroidism. FT4 levels were also seen to be significantly higher in the apathetic hyperthyroidism group compared to the classical hyperthyroidism group.[xxvi]

Indian Evidence: Clinical presentation of Hyperthyroidism in India

In Nijith and Ranjan 2022 cross-sectional study, Palpitation was found in 76.4% subjects. With regard to cardiovascular manifestations, no symptoms were seen in around 20% patients. Heat intolerance was present in 67.9% patients, followed by fatigue (65%) and weight loss 49.3%. Clinical examination revealed tachycardia in 80.7% patients, hypertension in 49.3% and wide pulse pressure in 36.4%. The mean heart rate was 105.8 and the mean pulse pressure was 58.3 mmHg. S1 auscultatory sound was loud in 27.9% of patients and systolic ejection murmur in the pulmonary area was seen in 17.1%. [xviii]

If a patient presents with a symmetrically enlarged thyroid, recent onset of orbitopathy characterized by chemosis, proptosis, conjunctival injection, lid lag, exposure keratitis and extra-ocular muscle dysfunction, and moderate to severe hyperthyroidism, Graves' disease (GD) is likely, and diagnosis may be based on clinical presentation only. Other characteristic symptoms include thyroid acropathy and pretibial myxedema. [xvi, xxvii]

S. No	Key summary point
1.	Hyperthyroidism may have a heterogenous presentation with symptoms manifesting across various organ systems. To avoid delay in diagnosis which leads to complications, a high degree of clinical suspicion is required. Any person with suspicion of hyperthyroidism must undergo thyroid function test. TSH <0.01 mIU/L with elevated free T4 and free T3 are indicative of overt hyperthyroidism

2.2 Serology

2.2.1 Thyroid Function Test

When there is a suspicion of hyperthyroidism in a clinical setting, it's imperative to verify it through biochemical tests such as observing low TSH levels, elevated free thyroxine (FT4), or heightened free tri-iodothyronine (FT3) levels.

Measuring serum TSH stands out as the most sensitive and specific blood test in assessing suspected thyrotoxicosis, making it the primary screening tool. However, in cases where thyrotoxicosis is strongly suspected, enhancing diagnostic accuracy is achieved by evaluating serum levels of TSH, free T4, and total T3 during the initial assessment.[xvi]

In cases of overt hyperthyroidism, serum levels of free T4, T3, or both are usually elevated, while serum TSH levels are typically decreased, often falling below 0.01 mIU/L. Notably, due to its higher concentration in the bloodstream, the free T4 assay generally offers greater sensitivity compared to free T3 assays, which aligns with anticipated results in clinical practice. [xvi]

The severity of hyperthyroidism can be gauged based on free T4 levels. Baseline T4 levels can also guide the dosing of the anti-thyroid drugs in the initial stage of management.

Indian Evidence: Reference range in India

In 2013 Study conducted in Delhi by Marwaha et al, in 4349 adults between the ages of 18 and 86 years (mean age 41.2 years) with normal thyroid function were recruited. Regardless of the age, the FT4 ranged from 10.1-24.8 pmol/L whereas the FT3 levels ranged from 2.4 to 8.8 pmol/L. The mean TSH value was 2.2+/-0.9 mIU/L [xxviii]

Indian Evidence: Role of the FT3/FT4 Ratio

Narkar et al remarked on diagnostic assays in India. They argued that although new generation TRAb assays are sensitive and specific for diagnosing Graves' Disease, however these tests are not widely accessible and have cost considerations. Further, destructive Thyrotoxicosis is diagnosed with the use of radionuclide scanning. 99mTc-pertechnetate [Technetium-99m sodium pertechnetate] or 131I-iodide [iodine-131 sodium iodide] are commonly used for diagnostic thyroid imaging in India. These investigations are not widely available, contraindicated in pregnancy and lactation and cannot be used in cases of iodine-containing drugs, food and contrast.

T3/T4 ratio <20 is suggestive of destructive thyrotoxicosis (DT) and >20 of GD. Results from Narkar et al revealed that in a cohort of 83 patients with overt hyperthyroidism: in patients with GD (n=22), 74% had T3/T4 ratio >20; in patients with DT (n=61), 73% had T3/T4 ratio < 20. It was determined that T3/T4 ratio had a sensitivity of 73.8%, specificity of 72.7% and diagnostic accuracy of 73.49%. [xxix]

It's crucial to identify the underlying cause of thyrotoxicosis. If the diagnosis isn't clear from the clinical presentation and initial biochemical assessment, further diagnostic testing is recommended. Depending on the expertise and resources available, this may involve:

- Assessing levels of TRAb (thyrotropin receptor antibodies)
- Examining thyroidal blood flow using thyroid ultrasonography
- Determining radioactive iodine uptake (RAIU)

In cases where clinical signs point towards a thyroid adenoma (TA) or a toxic multinodular goiter (TMNG), obtaining a 123I or 99mTc pertechnetate scan is advisable. These diagnostic steps help to pinpoint the specific etiology of thyrotoxicosis, guiding subsequent treatment decisions effectively. [xvi]

2.2.2 TRAb Immunoassay

Measurement of TSH receptor antibodies (TRAbs) using competitive-binding assays, such as TSH-R binding inhibitory immunoglobulins (TBII), is a sensitive and specific method for diagnosing Graves' disease. TRAbs, particularly thyrotropin-stimulating antibodies (TSAb), are valuable biomarkers for predicting extrathyroidal manifestations and fetal or neonatal hyperthyroidism. [xxx]

Currently there are two types of TRAb assays available. The Pros and cons are as follows:[xxxi]

Table 3: Comparison of Biological Assays and Thyroid Stimulating Hormone binding inhibition (TBII)

	Biological Assays	Thyroid Stimulating Hormone binding inhibition immunoglobulin (TBII)
Pros	• Differentiates between blocking and stimulating TRAb	• Is easy to perform and standardize • Results achieved in shorter duration • 2nd and 3rd generation TBII assays are very sensitive

		• Is commercially available
Cons	• Time consuming • May not be accessible as it a research-based testing • Is technically difficult	• Does not differentiate between blocking and stimulating TRAb • Dose not correlate with severity of illness

Commercial assays of thyroid antibody testing have pre-determined cut-offs for the diagnosis of Graves' disease.

TRAb is sensitive and specific assay for accurate diagnosis and monitoring of Graves' disease (GD). Sequential monitoring of TRAb can be used to guide duration of antithyroid drug (ATD) in GD patients.[xxxii] Negative or low-titer thyroid receptor antibody have a high likelihood of remission and can be used as the deciding factor to discontinue antithyroid drug treatment.[xxxiii]

TRAb assessment is crucial in pregnant women with suspected Graves' disease, history of GD, past treatments like radioactive iodine ablation or surgery, or previous instances of fetal thyroid dysfunction. Elevated TRAb levels, especially exceeding three times the upper limit of normal, necessitate close fetal monitoring and neonatal thyroid function assessment during pregnancy. TRAb assessment aids in the differentiation of hyperthyroidism originating from Graves' disease versus gestational hyperthyroidism, especially during the early stages of pregnancy. It can determine the necessity for antithyroid drugs (ATD) during the teratogenic period, ensuring the optimal health of both the mother and fetus. Initial TRAb levels should be measured in the first trimester, if elevated, is measured again at 18-22 weeks of gestation [xxx,xvi] If maternal TRAb concentration remains high (>3 times the cut off), monitoring of fetus for thyroid dysfunction throughout pregnancy is recommended. [xxxiv]

TRAbs play a crucial role in the pathogenesis and progression of Graves' ophthalmopathy/ orbitopathy (GO), serving as specific biomarkers. Measuring functional TRAbs, particularly TSAb, is vital for diagnosing, differentiating, and monitoring GO, which can provide valuable insights for effective disease management.[xxxv] Patients who are at high risk for deterioration of GO are associated with a high serum TRAb level.

Effect of biotin in thyroid evaluation: Caution must be exerted in patients who are on high dose (>100 mg/day) biotin supplementation (for hair and nails) which can lead to falsely high T3 and T4 levels and low TSH levels. Biotin may also result in false positive TRAb levels. Biotin should be stopped for a period of 2 to 7 days before testing can be employed. [xxxvi]

Indian Evidence: Utility of TSH Receptor Antibodies in India

In a study by John. M et al in Kerala, India, Graves' disease was differentiated from Non Graves' disease at presentation with the use of automated electrochemiluminescence TRAb immunoassay. TRAb tests's sensitivity/specificity of TRAb for diagnosing GD was 98.4%/62.9% at 1.75 IU/L (manufacturer cut off) and 91.2%/90.12% at 3.37 IU/L (study derived optimal threshold in Indian patients), respectively. [xxxvii]

2.3 Imaging

2.3.1 Thyroid Ultrasonography

Thyroid Ultrasonography (USG) is a diagnostic modality for assessing hyperthyroid patients that offers swift and non-invasive evaluation without exposing individuals to ionizing radiation. Its utility lies in determining cause of thyrotoxicosis and identifying thyroid nodules, with the quality of imaging depending on operator expertise and equipment quality, emphasizing the necessity of employing a high-frequency linear probe. GD often is recognized by diffuse thyroid enlargement and hypoechogenicity. Colour-flow or power Doppler examination aids in delineating vascular patterns and quantifying thyroid vascularity. In untreated GD, the thyroid vascularity is increased in multiple small areas which shows a pulsatile pattern entitled as "thyroid inferno". Elevated thyroid artery flow velocity and peak systolic velocity (PSV) are seen in untreated GD. The elevated PSV can distinguish GD from subacute thyroiditis or amiodarone-induced thyrotoxicosis type 2 where the blood flow is reduced.

USG findings combined with positive TRAb often obviate the need for scintigraphy, yet the latter remains useful in certain instances, especially before radioactive iodine (RAI) treatment. Ultrasonography with colour flow Doppler serves as a valuable alternative when RAI is contraindicated, offering insights into thyroid hyperactivity. Despite requiring meticulous adjustments, quantitative Doppler evaluation provides crucial data on thyroid function and

pathology through precise measurements of peak systolic velocity from intrathyroidal arteries, thereby contributing to comprehensive patient management. [ii,xvi]

Indian Evidence: Utility of Thyroid Ultrasonography in India

In a study by Malik et al in Srinagar India, to differentiate between 65 patients of GD(n=46) and thyroiditis (n=19), the peak systolic velocity of the inferior thyroid artery (PSV-ITA) using color flow Doppler Ultrasound was compared to technetium-99m pertechnetate thyroid uptake scan. Patients with GD had higher mean PSV-ITA. A cut off value of 30cm/sec was shown to have 91 sensitivity and 89% specificity. [xxxviii]

2.3.2 Thyroid Scintigraphy

Thyroid uptake Scintigraphy studies is recommended in the case of palpable thyroid nodules or if the etiology is unclear after TRAb testing. This is done using radioiodine uptake or technetium-99m pertechnetate.

Radioactive iodine uptake scans show a diffuse uptake in Graves' Disease, a focal uptake in toxic adenoma or nodules, absent/no uptake in thyroiditis, extra-thyroidal thyroid hormone production and in high iodine exposure cases.[xxxix]

In the evaluation of ectopic thyroid tissue and multiple thyroid nodules, positron emission tomography (PET)/ Single photon emission Computed Tomography SPECT/(-CT) or PET/SPECT/ ultrasonography may be an effective diagnostic tool. Technetium-99m-methoxyisobutylisonitrile or [^{99m}Tc] MIBI may assist in isolating the type of amiodarone induced thyroiditis.[xl]

8F-fluorodeoxyglucose (18F-FDG) PET scan (^{18}F-FDG-PET/CT scan) may have a role in the diagnosis of autoimmune thyroid disease (AITD) such as Graves' disease, Hashimoto's thyroiditis or atrophic autoimmune hypothyroidism. There is an increase in standardized uptake value in the thyroid parenchyma in these conditions. [xli]

S. No	Key summary point
2.	The etiology of hyperthyroidism must be delineated. Thyroid receptor antibody (TRAb) immunoassay is diagnostic for Graves' disease. Radioactive iodine uptake scintigraphy imaging shows differential pictures for Graves' disease, toxic

	multinodular goiter, toxic adenoma or thyroiditis. Thyroid ultrasonography enhanced with colour-flow or power doppler examination can help identify Graves' disease and thyroiditis.

3. Management of Hyperthyroidism

β-blockers offer temporary relief from symptoms of hyperthyroidism, they do not directly address the underlying thyroid dysfunction or its long-term effects. Beta-blockers antagonize the beta receptor mediated effects of catecholamines. These medications are commonly employed to regulate blood pressure, alleviate the rapid pulse sensation of palpitations, and reduce tremors and anxiety, since these manifestations are secondary to increased adrenergic activity.[xlii]

3.1 Role of Beta-blockers in initial management

In thyrotoxicosis, there is an increase in the expression of beta-receptors in the heart and other organs. As a result of the hyperadrenergic state due to upregulated beta-adrenergic receptors there is an increase heart rate, stroke volume, cardiac output, and contractility.[xliii,xliv]

Beta-adrenergic blockade is recommended for managing symptomatic thyrotoxicosis, in all patients, particularly targeting elderly individuals and those with resting heart rates exceeding 90 beats per minute or coexisting cardiovascular disease. However, beta-blockers are generally not recommended for patients with bronchospastic asthma. Alternatively, cardio-selective beta-blockers may be favoured, particularly in patients with asthma with close monitoring of the pulmonary status. Calcium Channel Blockers -Verapamil(240 mg oral or 5-10 mg intravenous)[xlv] and Diltiazem (60 mg, orally four times a day)[xlvi]- can offer rate control in patients who are not candidates for beta blockers. [xvi]

Table 4: Beta-Adrenergic Receptor Blockade in the Treatment of Thyrotoxicosis [xvi]

Drug[a]	Dosage	Frequency	Considerations
Propanolol	10-40 mg	3-4 times per day	Non-selective β-adrenergic receptor blockade Longest experience May block T4 to T3 conversion at high doses Preferred agent for nursing and pregnant mothers
Atenolol	25-100 mg	1-2 times per day	Relative β1 selectivity Increased compliance

			Avoid during pregnancy
Metoprolol[b]	25-50 mg	2-3 times per day	Relative β1 selectivity
Nadolol	40-160 mg	1 time per day	Non-selective β-adrenergic receptor blockade Once daily Least experience to date May block T4 to T3 conversion at high doses
Esmolol	IV pump 50 -100 µg/kg/min		In intensive care unit setting of severe thyrotoxicosis or storm

a- Each of these drugs are approved for treatment of cardiovascular diseases, but to date none has been approved for the treatment of thyrotoxicosis

b- Available in once daily preparation

While other β-blockers primarily target hyperthyroidism symptoms, propranolol offers a unique approach with its distinctive dual mechanism of action. The L-isomer of propanolol effectively blocks beta receptors, addressing symptoms like palpitations, anxiety, heat intolerance, and tremors. Meanwhile, the D-isomer inhibits thyroxine deiodinase, thereby impeding the conversion of T4 to T3 and providing some therapeutic benefit.[xlvii] In cases where high doses of propranolol (40 mg four times daily) are administered, there is inhibition of peripheral conversion of T4 to T3.[ii]

Beta-blockers are especially beneficial during the early stages before ATDs achieve their maximum therapeutic efficacy. However, beta blockers are only required for the initial symptomatic six to eight weeks as they do not appear to alter the synthesis or secretion of the thyroid hormones by the thyroid gland.[xlviii, xlix]

3.2 Management of Graves' Disease

The main goal in the management of Graves' Disease (GD) is to control hyperthyroidism by restoring normal thyroid hormone levels. Additionally, the presence of goiter and/or Graves' ophthalmopathy/ orbitopathy (GO) will impact treatment decisions. Patients and physicians have three effective options such as radioactive iodine (RAI) therapy, antithyroid drugs (ATDs), or thyroidectomy.[xvi] Surgery or RAI destroys the thyroid tissue in order to restore euthyroidism. ATD on the other hand prevents the thyroid hormone synthesis to gain euthyroidism thereby preserving the thyroid structure.[l]

Table 5: Candidates for Anti-Thyroid Drugs

Candidates for Anti Thyroid Drugs:
• Patients with high likelihood of remission (mild disease, small goiters, and negative or low-titer TRAb); • pregnancy; • the elderly or comorbidities increasing surgical risk or with limited life expectancy; • individuals in nursing homes or other care facilities • previously operated or irradiated necks; • lack of access to a high-volume thyroid surgeon; • moderate to severe active Graves' ophthalmopathy/ orbitopathy ; • Patients who need more rapid biochemical disease control.

3.2.1. Medical Management

ATDs represent the mainstay of therapy in most regions, including Europe, Asia, and the United States. It serves as the first-line treatment for GD, particularly in younger patients with mild or uncomplicated disease. ATDs includes thionamides, such as carbimazole (CBZ), methimazole (MMI), and propylthiouracil (PTU). These medications work by interfering with the function of thyroperoxidase, an enzyme crucial for iodide organification within the thyroid gland and inhibiting the coupling of iodotyrosines, thereby reducing the production of thyroid hormones. [ii]

Studies have shown that ATDs not only decrease thyroid hormone levels but also reduce TRAbs, a hallmark of GD which are responsible for the stimulation of the thyroid gland. Therefore, ATDs enhance remission rates compared to no treatment.[ii]

Carbimazole is the preferred first line ATD in non-pregnant individuals. Carbimazole has been available in India since 1963.[li] The Indian National List of Essential Medicines (NLEM) includes CBZ (5mg and 10mg) for wider accessibility, even at the primary healthcare level. [lii] Carbimazole offers a dose finer titration compared to methimazole[1]. This is an added advantage in the treatment of hyperthyroidism where carefully dose optimized treatment is required according to each patient's thyroid biomarkers. Carbimazole may even result in fewer cases of iatrogenic hypothyroidism and use of concomitant supplemental T4[2liii]

[1] Carbimazole doses of 60 mg, 45 mg, 40 mg, 30 mg, 25 mg, 20 mg, 15 mg, 10 mg and 5 mg have a Calculated active metabolite of 36 mg, 27 mg, 24 mg, 18 mg, 15 mg, 12 mg, 9 mg, 6 mg, and 3 mg which offers finer titration than methimazole (multiples of 5 mg and 10 mg)

[2] In Baek et al, one of the main reason for the change in ATD from methimazole to carbimazole was for further reduction in ATD dose. Carbimazole (n=38) with mean dose 2.3 mg (at the time of stopping of ATD) for a duration

While the mechanism of action of PTU is similar to that of carbimazole and methimazole, it offers an additional benefit when given in higher doses. It acts by inhibiting the peripheral conversion of thyroxine (T4) to the more potent triiodothyronine (T3). However, this effect is considered marginally beneficial except in cases of severe thyrotoxicosis. Furthermore, the shorter half-life of PTU compared to CBZ and MMI makes it less practical for long-term management. [ii]

3.2.2. Dosing, Titration and Duration [liv]

Dosing:

The initial dose of CBZ or MMI should be adjusted according to the severity of hyperthyroidism, and it should be roughly estimated based on the baseline levels of free T4 hormone.[lv]

Table 6: Initial dose of Anti-thyroid drugs in the treatment of hyperthyroidism[lvi]

Baseline Free T4 elevation	CBZ (mg)	MMI (mg)	PTU (mg)
1-1.5 x ULN	10-15	5-10	100-200
1.5-2 x ULN	20-30	10-20	200-400
2-3 x ULN	50-70	30-40	600-800

ULN – Upper Limit of Normal

Rationale for initial dose:

The reason behind determining the initial dose is rooted in how these medications work in the body, for example in the case of CBZ, it rapidly converts to methimazole, which tends to concentrate in the thyroid gland. Methimazole normally stays in the thyroid for about 20 hours. Starting with higher doses can help bring the disease under control faster, especially in cases where quick stabilization is necessary. [lvii, lviii]

Single dose Regimen for Carbimazole

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of 36 months compared to Methimazole (n=166) with mean dose of 3 mg for a duration of 30 months decreased the risk of relapse (HR 0.248, P = 0.004).

The anti-thyroid effects of carbimazole and methimazole are associated with their intrathyroidal actions where they remain in high concentrations for up to 20 hours. Single dose carbimazole in dose of 30 mg has been shown to be efficacious in the initial treatment of hyperthyroid Graves' disease patients with attainment of clinical euthyroidism and normalization of serum T4 levels within 1-3 months. A single daily dose of 30 mg in the initial regimen instead of multiple doses is convenient and can improve patient compliance.[lv,lvi,lix]

Indian Evidence: Carbimazole in Indian patients

In a 1992 Indian study by Gupta and Godbole in an area of mild iodine deficiency, patients administered single daily dose of 30 mg carbimazole(n=19) was compared with 10 mg carbimazole every 8 hours (n=14). Total T4, Total T3 and TSH were estimated at baseline and at 1,2,3,4, and 6 after treatment. Duration to euthyroidism was found to be similar in 30 mg OD (4.6 weeks) and 10 mg TID group (3.8 weeks) [p>0.05]. Therefore a single daily dose of carbimazole is comparable to multiple daily dose.[lx]

Titration:

After initiation of the treatment, thyroid function tests are often reviewed 3-4 weeks later to titrate the dose based on free T4 and free T3 levels. A significant proportion of patients achieve euthyroidism within this period. TSH levels often remain suppressed for several months and therefore do not provide a sensitive index of early treatment response. [ii]

The titration regimen is often preferred where dose is minimized in accordance with the cascading TFT results. Carbimazole is initially dosed at 10-40mg daily and titrated until maintenance of 5-15mg is achieved.[lxi, lxii] As anti-thyroid therapy is initiated, thyroid hormone secretion decreases, and the drug dose should be decreased to avoid hypothyroidism**.** [xx]

In Yap et al, after euthyroidism was achieved with a single daily dose of carbimazole in 24 patients; the maintenance phase of treatment was initiated. A single daily dose of 15 mg carbimazole was seen to be as effective as conventional doses of 5 mg thrice daily.[lxii]

Lowering the medication dosage without causing thyrotoxicosis to worsen indicates a reduction in disease activity. This may be due to a decrease in the production of TSH receptor autoantibodies

(TRAb). Additionally, the treatment goal shifts from complete inhibition of T4 and T3 synthesis to only partial inhibition.[xx]

TSH remains suppressed for first 6 months of treatment and therefore is an unreliable biomarker for early response of ATD treatment. [lxiii]

Certain factors can predict a low remission rate before beginning the treatment of thyroid-related conditions. These predictors include a large goiter, Graves' ophthalmopathy/ orbitopathy (GO), high thyroglobulin levels, high levels of TRAb and pretibial myxedema.[lv]

During the treatment, several factors can indicate poor responsiveness, such as persistently low TSH levels or high TSHR autoantibody (TRAb) levels. The duration of elevated TRAb can vary from patient to patient. Although the recommended treatment length is typically more than one year, persistently high TRAb levels beyond this period are the most useful predictor of a low remission rate.[lv]

Table 7: Duration Recommendation for Graves' Disease

ATA guidelines (2016) [xvi]	• If CBZ or MMI is chosen as the primary therapy for GD, the medication should be continued for approximately **12–18 months**. • Discontinue CBZ or MMI if TSH and TRAb levels are normal at that time.
ETA guidelines (2018)[ii]	• The optimal duration of ATD therapy for the titration regimen is **12–18 months**.
NICE guidelines (2019)[liv]	• When offering antithyroid drugs as first-line definitive treatment to adults with GD, CBZ should be offered for **12 to 18 months**. • Use either a block and replace or a titration regimen during this period. • Review the need for further treatment after 12 to 18 months.

<u>Rationale for 12-18 months' duration:</u>

Antithyroid drug therapy often leads to the normalization of TRAb levels over time in many patients, which plays a significant role in achieving remission after long-term treatment. [lvii,ii,l]

- TRAb titers typically decrease during antithyroid drug therapy and resolve in 70% to 80% of patients within 18 months of treatment.
- Reported remission rates, defined as achieving euthyroidism one year after discontinuing treatment are around 50%-55% after an initial 12 to 18 months of antithyroid drug therapy.
- However, if the patient continues to test positive for TRAb, the likelihood of remission is much lower, ranging from 0% to 20%.

According to McGregor et al.[l], the use of Carbimazole in patients with mild GD resulted in the inhibition of TRAb. The study demonstrated that CBZ directly impacted the autoantibody levels independent of its action on serum thyroxine which helped control hyperthyroidism. During the initial stages of CBZ treatment, both autoantibody levels and thyroid hormone levels decreased. However, after 6 weeks when thyroid hormone levels were maintained within the normal range with carbimazole and the use of T4 supplements, autoantibody levels continued to decrease over time.

In Garcia et al, patients who achieved euthyroid status at 10-12 months with low doses of antithyroid drugs were evaluated. In the group of patients where antithyroid drugs (carbimazole or methimazole: 2.5-5mg/day) in low doses was continued for a period of 5 years (N=53; Carbimazole (N=50); Methimazole (N=3)) the relapse rate was 22.64%. In the group that did not continue ATD after reaching euthyroidism at 10-12 months (N=31), the relapse rate was 77.42%. ($p<0.000$). [lxiv]

In Azizi et al, the efficacy of prolonged ATD administration in GD was investigated. The findings revealed that after a 5-year regimen of methimazole therapy, a persistent normalization of thyroid-stimulating hormone receptor antibodies (TRAb) was observed. Furthermore, the study noted that ATD treatment extending beyond 60 months yielded a remission rate of 85% over 4 years. The research concluded that long-term ATD therapy (>60 months) exhibited both safety and effectiveness, highest remission rates and often leading to the complete resolution of GD symptoms in most patients. [lxv, lxvi]

In a systematic review and meta-analysis by Azizi *et al.,* integrated findings from six studies with outcomes from long-term (>24 months) ATD treatment were analyzed. The annual remission rate for each year of treatment was found to be 16% [confidence interval (CI) 10–27%], showing a slightly higher rate in adults compared to non-adults (19% vs. 14%). Additionally, long-term ATD treatment exceeding 24 months induced a remission rate of 57% [CI 45–68%], showing a similar trend of higher rates in adults than in non-adults (61% vs. 53%). The complication rate was found to be 19.1% [CI 9.6–30.9%]. Major complications accounted for 1.5% of the total complications observed. [lxvii]

3.2.3. Low Dose Anti-thyroid Drug

An important aspect of medical management of patients with Graves' disease and Graves' Ophthalmopathy include prevention of iatrogenic hypothyroidism.[lxv] This may be achieved by reducing the antithyroid medications to a minimum of 2.5 mg during the maintenance phase.[lxviii] Furthermore, some people are extremely sensitive to low doses, therefore even 2.5-5 mg CBZ/day may be required to maintain control.[lxix]

Table 8: Evidence for low dose carbimazole for maintenance dose

Trabucco et al. [lxx]	66% patients with Graves' disease, a very low daily dose of carbimazole which was less than or equal to 5 mg was effective and had resulted a remission rate of 54%
Baek et al[liii]	Carbimazole was given in a mean dose of 2.3 mg for 3 years which resulted in relapse rate of 15.8%
Kon et al [lxxi]	Author describes 5 cases of Graves' disease, who on conventional doses 5 to 15 mg of carbimazole switched to hypothyroidism. In one patient fT4 showed a fluctuating yo-yo pattern. This also led to low normal or low fT4, low/mid normal serum TSH at normal fT3 levels. To maintain euthyroidism and to prevent rebound thyrotoxicosis patients were given Carbimazole 2.5 mg daily or 2.5 mg biweekly.

3.2.4. Block and Replace

The ‘block and replace’ therapy is an alternative to titration-based monotherapy. Upon achievement of euthyroidism, using Carbimazole (dosage 30-40 mg once daily), thyroxine replacement therapy (100-125 µg daily) is initiated. This is to prevent iatrogenic hypothyroidism and reduce the frequency of biochemical tests. Treatment may last six months, or it may be extended, particularly in the presence of significant thyroid ophthalmological disease. Some clinicians use this strategy in case of alterations in thyroid function throughout the treatment.[lvii]

Patients with Graves' Alternans, who alternate between hyperthyroidism and hypothyroidism status, may have thyroid stimulating hormone receptor (TSHR) blocking autoantibodies that fluctuate over time, which can be difficult to manage clinically. In cases where fluctuating hyperthyroidism and hypothyroidism is noted, block and replace antithyroid regimen can be used temporarily before considering definitive treatment.[lxxii,lxxiii]

3.2.5. Biochemical Goal of treatment

During every visit of follow up, dose of the anti-thyroid drug must be titrated and adjusted according to the free T4 and T3 levels. The serum concentration of the free T4 and T3 should be targeted to the middle range of normal values in non-pregnant adults with hyperthyroidism. Further, once the TSH has been normalized, it should be maintained within the reference range.[lxxiv]

3.2.6. Follow up [ii,xvi,liv]

Adults using antithyroid medications for hyperthyroidism should consider:

• Assessment of FT4 and total T3 levels 2-6 weeks after starting therapy to determine the severity of thyrotoxicosis and alter drug dosage accordingly

• Monitoring of serum T3 levels should also be done as free T4 levels may normalize despite persistent elevated serum total T3 levels

• Monitoring of TSH, FT4, and FT3 levels every 6 weeks until TSH is normalized

• Monitoring of TSH (with cascading) every 3 months until antithyroid medications are discontinued

• For patients undergoing long-term anti-thyroid drug (ATD) (>18 months), the interval can be extended to 6 months.

- For patients who have stopped ATD, consider routine monitoring with
    - TSH within 2 months of stopping ATD, then
    - TSH every 3 months for 1 year, then
    - TSH once a year

3.2.7. Adverse events and when to expect

Table 9: Adverse events associated with anti-thyroid drugs[lxxv]

Within the first few weeks of treatment initiation	Approximately 5 weeks	Within the initial 90 days of starting treatment
1. Minor side effects, such as pruritic rash and arthralgias, occur in roughly 5%. 2. Rash may resolve with continuous medication or with antihistamines, but it could be severe enough to need drug withdrawal. 3. Carbimazole/ methimazole may be switched to propylthiouracil, although 30% to 50% had a similar reaction.	1. Hepatotoxicity (Usually cholestatic) 2. Mean time to onset: 36 days 3. Incidence <0.1%	Agranulocytosis 1. Incidence is 0.3–0.6% with a mortality rate of 21.5% 2. Dose related adverse event 3. Can also occur owing to re-exposure to the medication after several years 4. Typical symptoms include high fever and severe pharyngitis. 5. Resolution: Immediate drug discontinuation, hospitalization, and provision of broad-spectrum antibiotics and hematopoietic

		growth factor treatment.

ATD therapy is definitively contraindicated in case of known significant adverse effects in the past.

Monitoring for adverse events:[ii,xvi,liv]

- Unless there is a suspicion of agranulocytosis or liver dysfunction, there is no requirement to routinely monitor the complete blood count and the liver function in patients who are on antithyroid drugs
- Patients need written instructions regarding the identification of symptoms of possible agranulocytosis which include sore throat, mouth ulcers, fever and the cessation of ATD treatment pending a differential white blood cell count

3.2.8. Medical Treatment Outcomes

Remission[xvi]

A patient is considered to be in the remission stage if they have had normal blood TSH, free T4, and total T3 for one year after discontinuing ATD therapy. Maximum remission rates (50-55%) are attained between 12-18 months.

TRAb levels should be measured before discontinuing ATD therapy because they help predict which individuals can be weaned off the medicine, with normal levels indicating a higher possibility of remission. Patients with consistently high TRAb levels after 12-18 months can continue Carbimazole/methimazole medication and retake the TRAb test after another 12 months, or they can have RAI or thyroidectomy.

Relapse/Recurrence after a course of ATD[ii]

Relapse is most frequent in the first 6-12 months after ATD cessation, but it can happen years later. Patients with severe hyperthyroidism, big goiters, or persistently high TRAb levels are more prone to relapse when medication is discontinued, although the prognosis is unpredictable. All patients should be thoroughly monitored for relapse during the first year after treatment, and at least once a year thereafter.

In patients who are contraindicated for anti-thyroid treatment, RAI and surgery options can be explored

3.2.9. Radioiodine therapy (RAI) in Graves' Disease

Candidates for RAI are Women planning a pregnancy in the future (in >6 months following RAI administration, provided thyroid hormone levels are normal), individuals with comorbidities increasing surgical risk, patients with previously operated or externally irradiated necks, lack of access to a high-volume thyroid surgeon, patients with contraindications to ATD use or failure to achieve euthyroidism during treatment with ATDs, patients with periodic thyrotoxic hypokalemic paralysis, right heart failure pulmonary hypertension, or congestive heart failure.[xvi]

Radioiodine therapy stands as the definitive treatment of choice for many countries, particularly for patients with small goiters (<50 g) or those with challenges in managing their condition with thionamides or facing contraindications to such drugs. The overarching therapeutic goal of Graves' disease is the induction of hypothyroidism in affected patients. This treatment effectively resolves hyperthyroidism in over 90% of patients afflicted with Graves' disease or autonomous thyroid nodules.[xvi,xxxvi]

However, several factors have been identified that may contribute to persistent hyperthyroidism following radioactive iodine treatment for Graves' disease. These include male gender, prior antithyroid drug therapy, prolonged treatment duration exceeding 6 months after diagnosis, elevated levels of FT4, larger thyroid volume, and heightened radioactive iodine uptake. Notably, achieving a euthyroid state before radioiodine therapy is recommended to mitigate the risk of radiation-associated thyroiditis, which can exacerbate thyroid hormone levels.[xvi,xxxvi]

For older patients and individuals with increased cardiovascular risk, it is recommended to administer β-blockers and initiate pretreatment with carbimazole or methimazole to mitigate the transient exacerbation of hyperthyroidism following radioiodine therapy. For this regimen, carbimazole or methimazole administration should be discontinued 2 to 7 days before treatment

and may be resumed 3 to 7 days afterward. Radioactive sodium iodide (Na131I) is administered orally and promptly accumulates in the thyroid gland. Subsequently, it induces significant tissue damage, resulting in the ablation of the thyroid gland and subsequent reduction in thyroid hormone levels within a period of 6–18 weeks. The dosage of ^{131}I may either be standardized (e.g., 10 mCi or 370 MBq) or tailored based on the size of the goiter and the uptake of radioiodine. Following the attainment of hypothyroidism, initiation of thyroid hormone replacement therapy is warranted.[xii,xvi,xxxvi]

Radioiodine treatment is contraindicated during pregnancy, lactation, and in patients with Graves' orbitopathy due to its potential to exacerbate the condition. Smokers, are at an increased risk of Graves' orbitopathy, and are also advised against radioiodine therapy. Moreover, radioiodine therapy may exacerbate or induce eye disease in patients with Graves' disease, particularly those who smoke or have high TRAb levels. To mitigate this risk, pretreatment with prednisone, tapered over 3 months, is recommended for smokers, individuals with elevated TRAb levels, or those with preexisting thyroid eye disease.[xii,xvi,xxxvi]

Monitoring of RAI treatment[xvi,xlviii]

Following radioactive iodine treatment, it is recommended to monitor thyroid function in adults closely by measuring TSH, FT4, and FT3 levels, every 6 weeks for the initial 6 months until TSH levels are normalized. In adults who develop hypothyroidism post-treatment and are not taking ATDs, levothyroxine replacement therapy should be initiated. The starting dosage varies based on age and cardiovascular history. Adults aged <65 years with primary hypothyroidism and no history of cardiovascular disease may be given levothyroxine (1.6 micrograms/kg body weight/day), rounded to the nearest 25 micrograms. Conversely, for adults aged ≥65 years or those with a history of cardiovascular disease, levothyroxine (lower dosage of 25-50 micrograms/ day) with titration is advised. While treating primary hypothyroidism with levothyroxine, the goal is to maintain TSH levels within the reference range. If symptoms persist, adjusting the dose of levothyroxine further may be necessary to achieve optimal well-being. However, caution should be exercised to avoid doses that cause TSH suppression or thyrotoxicosis.

It is important to note that it can take up to 6 months for TSH levels to return to the reference range, especially in individuals with very high initial TSH levels or a prolonged period of untreated hypothyroidism. Therefore, adjustments to the levothyroxine dose should consider this duration.

For adults with TSH levels within the reference range 6 months after radioactive iodine treatment, consider measuring TSH at 9 and 12 months after treatment. If TSH levels remain within the reference range 12 months following treatment, these should be monitored every 6 months unless hypothyroidism is developed. In cases where hyperthyroidism persists after RAI treatment, consider using ATDs until the 6-month visit. If hyperthyroidism is present after 6 months of treatment, further treatment choices should be explored.

3.2.10. Surgery

Candidates for Surgery in the management for Graves' disease include women planning a pregnancy in <6 months provided thyroid hormone levels are normal, symptomatic compression or large goiters (≥80 g); low uptake of RAI; when thyroid malignancy is documented or suspected, large thyroid nodules especially if >4 cm or if nonfunctioning, or hypofunctioning on 123I or 99mTc pertechnetate scanning; coexisting hyperparathyroidism requiring surgery especially if TRAb levels are particularly high; moderate to severe active Graves Ophthalmopathy.[xvi]

Surgery (thyroidectomy) offers a definitive option for some patients of Graves' disease. Thyroidectomy ensures a swift return to a euthyroid state but carries a low risk of complications (around 1-2%) like bleeding, infection, or recurrent laryngeal nerve damage affecting the voice. Complications are fewer if thyroidectomy is being performed by experienced surgeons.[xvi] Total thyroidectomy is the preferred surgical approach for GD because it minimizes the chance of hyperthyroidism recurring compared to a subtotal thyroidectomy. However, this procedure necessitates lifelong thyroid hormone replacement therapy to compensate for the absence of thyroid gland function. In preparation for surgery, patients are brought to a euthyroid state with antithyroid drugs and also β-blockers are used to control cardiac rhythm. Additionally, vitamin D and calcium supplementation may be given to prevent postoperative hypocalcemia especially in patients who are at high risk of parathyroid injury .[xvi] Following thyroidectomy, thyroid hormone

replacement therapy is initiated to manage the hypothyroid state, with serum TSH levels monitored every 4–6 weeks postoperatively to adjust dosing as needed.[xvi]

S. No	Key summary point
3.	In cases of symptomatic thyrotoxicosis, it is necessary to initiate beta-blockers (unless contraindicated in which case calcium channel blockers are recommended) especially in patients with co-morbidities. Beta-blockers is recommended in the initial symptomatic thyrotoxic phase for a period of 6-8 weeks. Propanolol in doses of 10-40 mg given in a frequency of 3 to 4 times per day is recommended.
4.	In diagnosed patients with Graves' disease, the first line of therapy is anti-thyroid drugs. Carbimazole is the preferred anti-thyroid drug in India in non-pregnant hyperthyroidism patient.
5.	In patients with Graves' disease, the titration regimen in preferred over block and replace regimen for most cases. Initial dose is determined based on the free T4 levels and lead to normalization of free T4 within 4-6 weeks. From the initial dose, the dose is serially down titrated to the lowest maintenance dose depending on the cascading thyroid function tests every 6 weeks-3 months.
6.	The lowest maintenance dose of carbimazole may be in the range of 2.5 mg to 10 mg
7.	In Graves' disease, during follow-up in titration regimen, dose of anti-thyroid drug must be titrated and adjusted according to free T4 and free T3 levels. The serum concentration of the free T4 and free T3 should be targeted to the middle range of normal values. TSH is an unreliable biomarker for early response of the ATD treatment. Once the TSH normalizes, it should be maintained within the reference range.
8.	Anti-thyroid drugs must be continued for a period of 12 to 18 months for achieving maximum remission rate of 50-55%. Review for continuation of carbimazole must be undertaken after 12 to 18 months of treatment
9.	Antithyroid drugs may be given for more than 5 years in low maintenance dose. Long term ATD have led to a remission rate of 85% with a good safety profile. For patients undergoing long term treatment with ATD (> 18 months), the follow up interval can be 6 months
10.	For patients who have stopped ATD treatment, consider routine monitoring with TSH within 2 months of stopping ATD, then every 3 months for 1 year and then annually
11.	ATD therapy is contraindicated in case of known significant adverse effects in the past.
12.	A baseline complete blood count including white blood cell count and differential count and liver function test must be done prior to initiating ATD.

13.	Patients need written instructions regarding the identification of symptoms of possible agranulocytosis which include sore throat, mouth ulcers, fever and the cessation of ATD treatment pending a differential white blood cell count
14.	Unless there is a suspicion of agranulocytosis or liver dysfunction, there is no requirement to routinely monitor the complete blood count and the liver function in patients who are on antithyroid drugs
15.	In patients requiring radioactive iodine (RAI) treatment, it is recommended to administer beta-blockers and initiate pretreatment with anti-thyroid drugs to mitigate the transient exacerbation of hyperthyroidism following radioiodine therapy. For this regimen, carbimazole or methimazole administration should be discontinued 2 to 7 days before treatment and may be resumed 3 to 7 days afterward.
16.	The dosage of ^{131}I may either be standardized (e.g., 10 mCi or 370 MBq) or tailored based on the size of the goiter and the uptake of radioiodine. Following the attainment of hypothyroidism, initiation of thyroid hormone replacement therapy is warranted.
17.	Radioiodine treatment is contraindicated during pregnancy, lactation, and in patients with Graves' orbitopathy due to its potential to exacerbate the condition. Smokers, are at an increased risk of Graves' orbitopathy, and are also advised against radioiodine therapy.
18.	Following radioactive iodine treatment, it is recommended to monitor thyroid function in adults closely by measuring TSH, FT4, and FT3 levels, every 6 weeks for the initial 6 months until TSH levels are normalized.
19.	Total thyroidectomy is the preferred surgical approach for GD because it minimizes the chance of hyperthyroidism recurring compared to a subtotal thyroidectomy. Complications are fewer if thyroidectomy is being performed by experienced surgeons. In preparation for surgery, patients are brought to a euthyroid state with antithyroid drugs and β-blockers.

3.3 Graves' Ophthalmopathy/Orbitopathy

Graves' ophthalmopathy/ orbitopathy (GO), also known as thyroid eye disease (TED) or thyroid-associated orbitopathy (TAO), is an inflammatory autoimmune illness that affects about 25% of Graves' disease (GD) patients. GO primarily affects young women. It typically begins between the third and fourth decades of life, and its clinical manifestation may be more severe in senior persons and men, and milder in the Asian population. Mild and non-progressive cases are more common, whereas moderate-to-severe forms account for only 5-6%.**Error! Bookmark not defined.**[lxiv] Although GO is self-limiting in the majority of patients, it can be profoundly disabling due to its impact on vision and appearance, resulting in a considerable loss in quality of life.[lxxvi,lxxvii]

Indian Evidence: Graves' Orbitopathy in India

Reddy et al. [lxxviii] *conducted a study in the referral center of North India. The study reported a Graves' ophthalmopathy prevalence of 28%(65 patients) among 235 newly referred patients with Graves' disease with a similar distribution between males (28%) and females (27%). The condition was mild in 83%, moderate-severe in 15%, and sight-threatening in 2% of patients and only two (3%) instances had active ophthalmopathy. The most common presentation was upper eyelid retraction (83%), followed by exophthalmos (75%).*

3.3.1. Management of Graves' ophthalmopathy/ orbitopathy: [ii,xvi,lxxvii]

The choice of treatment for Graves' ophthalmopathy/ orbitopathy is determined based on the clinical activity, severity, and disease duration since anti-inflammatory or immunosuppressive treatments are less effective after 18 months of disease duration.

Patients at risk of deterioration including clinically active Graves' ophthalmopathy/ orbitopathy, smokers, severe/unstable hyperthyroidism, and high serum thyrotropin receptor antibody (TRAb) titers must be referred to combined thyroid-eye clinics or specialized centres with endocrine and ophthalmic expertise for an accurate and timely diagnosis to improve prognosis and quality of life.

All patients with Graves' hyperthyroidism, regardless of the presence or absence of Graves' ophthalmopathy/ orbitopathy should be encouraged to avoid smoking. Counselling and therapy options for moderate to severe, active Graves' ophthalmopathy/ orbitopathy (GO) should be discussed with the patients.

Medical management:

Comparison of different treatment modalities for Mild, Moderate-severe, and Severe Graves' ophthalmopathy/ orbitopathy (GO)

Mild Graves' ophthalmopathy/ orbitopathy (GO): [ii]Error! Bookmark not defined. Mild GO should be treated with local treatments and risk factor control measures. Mild and inactive GO can be treated based on the patient's preference along with the standardized criteria.

Patients with mild and active GO of recent onset should receive a 6-month selenium supplementation to improve eye-related manifestations and quality of life and prevent progression

to more severe forms. Treatment with antithyroid drugs (ATDs) or thyroidectomy is recommended for hyperthyroidism; prophylactic treatment with prednisone/prednisolone may be considered only in patients undergoing RAI.

Moderate to severe Graves' ophthalmopathy/ orbitopathy GO: [ii, lxxvii]

Mycophenolate sodium (or mofetil) is the primary treatment for moderate-to-severe and active GO. For moderate-to-severe and active GO, including constant and inconstant diplopia, severe inflammatory signs, and exophthalmos > 25 mm, intravenous (IV) methylprednisolone at the highest cumulative dose (7.5 g per cycle) as monotherapy is a valid first-line treatment.
A 1-year follow-up study of previously untreated patients with moderate-severe GO demonstrated that although a low dose of prednisolone was well tolerated, IV pulse methylprednisolone (0.5 g given thrice a month for 4 months) was more effective compared to oral prednisolone 1mg/kg/day for 6 weeks.[lxxix]

If primary treatment fails and there is no improvement in the severity of GO, second-line treatments after evaluating ocular and biochemical factors (liver enzymes) such as IV methylprednisolone monotherapy with high single doses (0.75 g) and a maximum cumulative dose of 8 g each cycle, oral prednisolone or prednisolone in combination with cyclosporine or azathioprine, orbital radiotherapy combined with oral or IV glucocorticoids, azathioprine, rituximab, or tocilizumab are recommended for moderate-to-severe and active GO. Prednisone or prednisolone prophylaxis should be used if RAI treatment is chosen and in the presence of risk factors such as smoking and high TRAb.[lxxvii]

Li *et al.*[lxxx] performed a network meta-analysis to identify 15 trials in an attempt to compare the effects of various treatment modalities on active, moderate-to-severe GO. IV glucocorticosteroids at low (4.5-5 g), moderate (6 g), and high (7-8 g) cumulative dosages outperformed oral glucocorticosteroids in improving the overall response rate. They further validated that the cumulative low dose (4.5 - 5 g) was the most appropriate regimen during the evaluation of efficacy and safety outcomes. An average IV glucocorticoid dose of 3.8 g was reported by an Indian study by Gupta et al. that investigated visual morbidity in patients with GO.[lxxxi]

Another meta-analysis consisting of 12 trials and 448 patients, suggested that tocilizumab provided significant reduction in proptosis and was a safe drug of choice followed by rituximab.[lxxxii]

For moderate-to-severe and active GO, ATDs should be used to manage hyperthyroidism until the treatment for GO treatment is completed.

Sight-threatening Graves' ophthalmopathy/ orbitopathy: [ii,xvi,lxxvii]

High doses of IV methylprednisolone (0.5-1 g daily for three days or every second day) should be administered immediately in patients with ophthalmic neuropathy. In case of a lack of improvement within 1-2 weeks, urgent orbital decompression should be performed. Further patients with recently developed ocular subluxation, should also undergo orbital decompression on an urgent basis. Severe corneal exposure should be rapidly treated medically or with more intrusive procedures to minimize progression to corneal breakdown, which should be surgically corrected immediately.

Due to the serious nature of the disease, treating GO should be prioritized while ATDs can be used to control hyperthyroidism during this period. ATD treatment given in the long term is beneficial in patients with GO due to decline of the serum TRAb levels as well as normalization of the thyroid function. Caution must be undertaken to avoid hypothyroidism of iatrogenic cause in such patients.[lxxvii]

S. No	Key Summary Point
20.	Patients at risk of deterioration including clinically active GO, smokers, severe/unstable hyperthyroidism, and high serum thyrotropin receptor antibody (TRAb) titers must be referred to combined thyroid-eye clinics or specialized centers with endocrine and ophthalmic expertise for an accurate and timely diagnosis to improve prognosis and quality of life
21.	Due to the serious nature of the disease, treating GO should be prioritized while ATDs can be used to control hyperthyroidism during this period. ATD treatment given in the long term is beneficial in patients with GO due to decline of the serum TRAb levels as well as normalization of the thyroid function.
22.	Patients with mild and active GO of recent onset should receive a 6-month selenium supplementation to improve eye-related manifestations and quality of life and prevent progression to more severe forms. Treatment with antithyroid drugs (ATDs) or thyroidectomy is recommended for hyperthyroidism;

23.	Mycophenolate sodium (or mofetil) is the primary treatment for moderate-to-severe and active GO. For moderate-to-severe and active GO, including constant and inconstant diplopia, severe inflammatory signs, and exophthalmos > 25 mm, intravenous (IV) methylprednisolone at the highest cumulative dose (7.5 g per cycle) as monotherapy is a valid first-line treatment.
24.	High doses of IV methylprednisolone (0.5-1 g daily for three days or every second day) should be administered immediately in patients with ophthalmic neuropathy. In case of a lack of improvement within 1-2 weeks, urgent orbital decompression should be performed. Further patients with recently developed ocular subluxation, should also undergo orbital decompression on an urgent basis. Severe corneal exposure should be rapidly treated medically or with more intrusive procedures to minimize progression to corneal breakdown, which should be surgically corrected immediately.

3.4 Multinodular Goiter

Multi-nodular goiter is prevalent in areas where there is prevalence of mild to moderate iodine deficiency. It is more frequently observed in women and typically manifests during the fourth and fifth decades of life [lxxxiii]

Diagnosis and assessment[xii,xvi]

Multinodular goiter can be characterized by subclinical hyperthyroidism for a long duration which precedes the development of clinical signs and symptoms. The clinical signs associated with multinodular goiter are milder compared to Graves' disease. Arrythmia and atrial fibrillation are commonly associated with multi-nodular goiter. Thyroid scintigraphy scans are useful for assessing thyroid nodularity showing an uneven radionuclide distribution of numerous hyperfunctioning and cold nodules in toxic multinodular goiters (TMNG). Ultrasonography can help identifying the size and number of nodules whereas the colour doppler can give an estimate of the vascularity. To exclude malignancy in the cold nodules, FNAC may be indicated. CT and MRI may help to delineate retrosternal and recurrent enlargement of the thyroid gland.

Management Recommendations[xii,xvi]

<u>Symptomatic treatment</u>

Beta-adrenergic blockade is recommended in all symptomatic thyrotoxicosis patients, particularly those with resting heart rates over 90 bpm or coexisting cardiovascular disease. Caution is advised in patients with bronchospastic asthma, where beta-blockers are generally contraindicated; alternatively, relative beta-1 selective agents can be used with careful monitoring. Calcium channel blockers like verapamil (240 mg oral or 5-10 mg intravenous) [xlv] or diltiazem (60 mg, orally four times a day)[xlvi] can be administered for rate control in patient's intolerant to or unsuitable for beta-blockers.

Beta-blockers in asymptomatic patients who are at a high risk for complications is required if radioiodine is the mode of treatment. This is because the RAI may lead to a transient worsening of hyperthyroidism in patients with TMNG or TA.

Treatment for Multinodular Goiter[xvi]

For toxic multinodular goiter (TMNG), treatment options include radioactive iodine (RAI), thyroidectomy, or low-dose methimazole (MMI) in some cases. RAI and surgery swiftly eliminate hyperthyroidism, with RAI achieving 50%-80% response rates in TMNG and surgery resulting in prompt euthyroidism in TA. Factors guiding treatment selection include age, comorbidities, goiter size, and patient preference. RAI is preferred in patients with older patients, prior surgery or scarring in the anterior neck, small goiter size, lack of access to surgery and a RAIU that is sufficient to allow therapy. Contraindications to RAI include pregnancy or women planning pregnancy within 6 months, lactation, coexisting thyroid cancer, patients who will not be able to follow the radiation safety guidelines.

Prior to RAI, pre-treatment with beta-blockers and ATD must be given to prevent complications. Sufficient RAI in a single dose should be administered to alleviate hyperthyroidism in TMNG. Follow-up for thyroid function test (free T4, total T3 and TSH) is evaluated after the RAI is within 1-2 months of treatment. Thereafter, biochemical monitoring is at every 4 to 6 week intervals for 6 months. If the patient becomes hypothyroid, monitoring is continued till patient stabilized on thyroid hormone supplementation. If hyperthyroidism persists after 6 months, retreatment with RAI is suggested.

Surgery by a high-volume surgeon is preferred in patients who have compressive symptoms or signs, coexisting thyroid cancer concern. Coexisting hyperparathyroidism that requires surgery, a

large goiter size (>80g), retrosternal or substernal extension, and need immediate hyperthyroidism resolution Surgery is not recommended in certain comorbidities such as cardiopulmonary disease, debilitating disorders such as cancer, and lack of access to a high volume surgeon. In pregnancy, surgery must be considered only if patient is uncontrolled on ATD or rapid control is required.

If surgery is the chosen modality of treatment, pretreatment with ATD is required for achieving euthyroidism. Beta-blockers in surgery are required in symptomatic patients as well as patients at risk of complications. Beta-blockers can be slowly discontinued following the surgery. Near-total or total thyroidectomy is the preferred surgical approach. Post-thyroidectomy, serum calcium with or without iPTH levels should be measured. Based on the measured levels oral calcium and calcitriol supplementation may be needed.

After thyroidectomy, thyroid hormone supplementation must be initiated with TSH measured every 1-2 months until the patient is stable. Monitoring must be continued annually thereafter. In case of persistence of hyperthyroidism, RAI should be used for retreatment. For select patients in whom RAI or surgery are not feasible, alternative therapies such as ethanol or radiofrequency ablation may be considered, provided expertise in these procedures is available.

Long-term Antithyroid drug[lxxxiv] A clinical study compared the effectiveness of long-term methimazole (LT-MMI) versus radioactive iodine (RAI) treatment in managing hyperthyroidism in patients with toxic multinodular goiter (TMNG). The study demonstrated that LT-MMI therapy led to earlier attainment of euthyroidism and longer sustained normal serum thyrotropin levels compared to RAI treatment. Additionally, no major treatment-related adverse events were observed in either group.

3.5 Toxic Adenoma

Thyroid adenomas are non-cancerous growths found in the thyroid gland. While some are dormant, others produce thyroid hormones. When they are hormonally active, they are known as toxic thyroid adenomas[xvii]

Diagnosis and assessment[xii,xvi,xvii]

Thyroid adenomas are sporadic in nature and occur more in females. Thyroid adenomas are associated with iodine deficiency. Around 1% of patients with thyroid adenoma have hyperthyroid symptoms. Commonly thyroid adenoma patients are asymptomatic, may have a visible or palpable thyroid mass, and rarely have dyspnea, dysphagia, and hoarseness of voice. Thyroid function tests, thyroid ultrasound(to distinguish adenoma from carcinoma- carcinoma may be identified by irregular margins, microcalcifications, hypoechogenicity, absent halo sign, and increased intramodular blood flow), fine needle aspiration biopsy(for adenoma with high suspicion of malignancy), iodine-123 (to distinguish between a hyperfunctioning and a hypofunctioning nodule) and genetic evaluation in some cases may be required for diagnostic evaluation.

Management Recommendations[xvi,liv,xvii]

Symptomatic treatment will be similar to that of toxic multinodular goiters (TMNG).

Treatment of Toxic Adenoma

RAI and surgery are the therapeutic options for toxic adenoma. Pretreatment with anti-thyroid drug and beta-blockers are needed in patients especially in those with high risk of complications.

RAI is preferred in patients with older patients, prior surgery or scarring in the anterior neck, small goiter size, lack of access to surgery and a RAIU that is sufficient to allow therapy. RAI needs to be given in a single sufficient dose. Follow-up for thyroid function test (free T4, total T3 and TSH) is evaluated after the RAI is within 1-2 months of treatment. Thereafter, biochemical monitoring is at every 4 to 6 week intervals for 6 months. If the patient becomes hypothyroid, monitoring is continued till patient stabilized on thyroid hormone supplementation. If hyperthyroidism persists after 6 months, retreatment with RAI is suggested.

Surgery by a high-volume surgeon is preferred in patients who have compressive symptoms, need to avoid radiation, and need immediate hyperthyroidism resolution. Following evaluation via ultrasound, an ipsilateral thyroid lobectomy or isthmectomy is performed in cases of isolated thyroid adenomas. Post-surgical monitoring following lobectomy includes TSH and free T4 after 4-6 weeks. Persistent rise in TSH levels requires thyroid hormone supplementation.

Evidence for Surgery and RAI in hyperthyroid patients including multinodular goiter and toxic adenoma

A clinical study compared various preoperative preparation regimens for hyperthyroid patients undergoing thyroidectomy, excluding iodine preparations. Among 168 patients studied, procedure time, hospital stay duration, and overall complication rates were higher compared to euthyroid patients, though operative blood loss did not significantly differ. The study suggests that iodine preparations may not be necessary for preoperative preparation, with lithium carbonate showing efficacy for refractory hyperthyroidism, and no significant difference in post-thyroidectomy complication rates between patients receiving thionamides alone or in combination with β-blockers[lxxxv]

Additionally, a retrospective review of 325 hyperthyroidism patients managed surgically from 1990 to 2005 revealed varied etiologies including Graves' disease (185), toxic multinodular goiter (105), and autonomously functioning thyroid nodules (35). Surgical indications included large goiter, relapse after antithyroid drug therapy (ATD), and presence of nodules. Total thyroidectomy post-1995 provided immediate and permanent cure with negligible mortality and acceptable morbidity, suggesting surgery as a viable option for hyperthyroidism management, especially in experienced hands[lxxxvi]

Findings from the evaluation of radioiodine therapy in 130 toxic multinodular goiter patients showed successful reversal of hyperthyroidism in 87% (low doses of RAI) and 82% (high doses of RAI) of patients. Hypothyroidism rates were 5% in the low-dose and 12.5% in high-dose group, respectively with no significant difference in total dose per gram of thyroid tissue. However, Group II, receiving calculated high doses, required fewer administrations and achieved hypothyroidism faster, suggesting lower post-therapy hypothyroidism incidence with low doses. [lxxxvii]

Results from a 20-year retrospective study on 3891 hyperthyroid patients revealed high remission rates with low-dose I-131 therapy (LDT), particularly within 12 weeks and predominantly among treatment-naïve patients with Graves' disease, toxic multinodular goiter, or autonomous toxic nodule. Factors such as lower free T4 levels, smaller goiter size, and shorter duration from hyperthyroidism onset to LDT correlated with higher remission rates, suggesting LDT's efficacy as a primary management option for hyperthyroidism[lxxxviii]

S. No	Key Summary Point
25.	Thyroid scans are useful for assessing thyroid nodularity, with different patterns observed in toxic adenomas (TA), and toxic multinodular goiters (TMNG).
26.	In patients with TMNG and TA Beta-adrenergic blockade is recommended in all symptomatic thyrotoxicosis patients, particularly those with resting heart rates over 90 bpm or coexisting cardiovascular disease. Caution is advised in patients with bronchospastic asthma, where beta-blockers are generally contraindicated; In patients where RAI is the modality of treatment, beta-blockers is indicated even in asymptomatic patients and in patients at high risk of complications.
27.	MNG and TA patients with overt hyperthyroidism should be rendered euthyroid with carbimazole or methimazole before definitive treatment. The modality of treatment recommended are RAI, surgery or long term ATD.

4. Thyroiditis

Thyroiditis may exhibit temporary thyrotoxicosis as a component of their classic triphasic course: thyrotoxicosis, hypothyroidism, and eventual recovery. Types of thyroiditis include subacute thyroiditis, painless (silent) thyroiditis, acute (suppurative) thyroiditis, palpation (traumatic) thyroiditis, postpartum thyroiditis, and drug-induced thyroiditis. Thyroid dysfunction resulting from thyroiditis tends to be less severe compared to endogenous thyrotoxicosis.

Subacute thyroiditis

Subacute thyroiditis (de Quervain thyroiditis), presents with thyroid pain, typically radiating to the ears, jaw, or throat. Diagnosis involves clinical history (malaise, low-grade fever, fatigue and history of viral infection), physical exam, lab tests, and radioactive iodine uptake. The thyroid may be slightly enlarged, firm, and tender. About 50% of cases have an initial thyrotoxic phase due to thyroid hormone release from damaged follicular cells lasting for 3–6 weeks, followed by a hypothyroid phase in about 30% of patients that can persist for up to 6 months and a return to a euthyroid state within 12 months. Five to fifteen percent may develop persistent hypothyroidism, and recurrence rates of 1%–4% have been reported.[xvi]

Thyroid pain/tenderness, elevated erythrocyte sedimentation rate (ESR), hyperthyroidism, hypoechoic ultrasound pattern, low uptake on thyroid scan, and specific findings on fine-needle

aspiration can help in diagnosing subacute thyroiditis (SAT). Women are more predisposed to developing SAT and subsequent hypothyroidism.[lxxxix] Additional findings include presence of C-reactive protein levels, as well as mild anemia and increased white blood cell (WBC) count. About 25% of patients may have reduced levels of antithyroid antibodies. Radioactive iodine uptake (RAIU) and thyroid scintigraphy results are low, with thyroid ultrasound showing diffuse heterogeneity, focal hypoechoic areas, and decreased or normal color flow Doppler.

Therapy for initial mild symptomatic subacute thyroiditis with beta-adrenergic-blocking drugs and nonsteroidal anti-inflammatory agents (NSAIDs) should be considered. [xvi] Average time for pain resolution with NSAIDs is 5 weeks (with a range of 1–20 weeks). If patients do not respond to initial treatment with full dose of NSAID or present with moderate to severe pain and/or thyrotoxic symptoms, corticosteroids should be considered: prednisone at a dosage of 40 mg daily for 1–2 weeks, followed by a gradual taper over 2–4 weeks or longer based on individual clinical response. Antithyroid drugs (ATDs) are not recommended for the treatment of subacute thyroiditis.[xvi]

Painless thyroiditis

Painless or silent thyroiditis lacks the prodrome, neck pain, or elevated ESR, WBC count, or C-reactive protein. Commonly observed during the postpartum period, painless thyroiditis can also occur in nonpregnant women and men, as well as in certain drug-induced thyroid dysfunction cases such as those associated with lithium or cytokine therapy. A small, non-tender goiter is often present. 5%–20% of patients experience the thyrotoxic phase, lasting around 3–4 months, while the hypothyroid phase is more prevalent or more frequently identified, lasting up to 6 months. Most patients regain normal thyroid function within 12 months, but persistent hypothyroidism affects 10%–20% of individuals. Recurrence rates are approximately 5%–10%.[xvi]

Painless thyroiditis likely represents an autoimmune disorder, as evidenced by the presence of positive anti–thyroid peroxidase antibodies in 50% of patients, along with lymphocytic infiltration histopathologically. [xvi] Symptomatic individuals should receive treatment with beta-adrenergic-blocking drugs to alleviate symptoms. Antithyroid drugs (ATDs) are not effective in this context, as there is already minimal new hormone synthesis in these patients. In rare severe cases, corticosteroids may be considered as a therapeutic option.[xvi]

Acute thyroiditis

Treatment for acute thyroiditis involves antibiotics and, in some cases, surgery with Beta-blockers for symptomatic management. Patients identified with acute thyroiditis, also recognized as suppurative thyroiditis or thyroid abscess, commonly display normal thyroid function (euthyroid). Antithyroid drugs (ATDs) are not warranted in the treatment of this condition.[xvi]

Amiodarone Induced Thyrotoxicosis

Amiodarone induced thyroiditis is commonly (AIT) seen in iodine deficient regions and in the male gender. AIT presents with typical symptoms of hyperthyroidism except the cardiac symptoms may differ due to underlying condition. If a patient stable on amiodarone, suddenly undergoes re-emergence of cardiac condition such as worsening of atrial fibrillation and palpitation, AIT must be suspected. In some cases, cardiac symptoms are the only clinical evidence for AIT. Thyroid function testing is recommended to such a patient.[xc, xci]

There are two types of AIT: AIT 1 and AIT 2.

Amiodarone Induced Thyrotoxicosis 1 (AIT 1) often occurs when there is an underlying thyroid disease such as multinodular goiter and Graves' disease. AIT 1 is common in iodine deficient regions. Since Amiodarone contains iodine which may cause iodine excess and lead to increased thyroid hormone biosynthesis, AIT 1 may occur. AIT 1 usually appears after around three months of starting Amiodarone. In the thyroid scintigraphy scans, I-131 uptake is high. In thyroid ultrasonography, a diffuse or nodular goiter pattern may be seen. Vascularity on Echo-color Doppler ultrasound if often increased. The T4/T3 ration is <4. Antibodies such as TgAb, TPOAb and TSI may be present in AIT 1. Interleukin-6 levels are often normal. High dose ATD (methimazole – 30-40 mg/day; carbimazole 20-60 mg/day[xcii, xciii] or propylthiouracil 400-600 mg/day) is given to block thyroid hormone synthesis. The dose is tapered to a low maintenance dose. Amiodarone should be stopped if feasible. In this case, ATDs are continued for the next 6 to 18 months and then discontinued based on the urine iodide levels. If amiodarone is continued, the patient must remain on the ATD. A modest response to ATD is expected since the iodine uptake levels are high. $KClO_4$ (potassium perchlorate) may be used to supplement the antithyroid drugs due to its iodine uptake blocking action. $KClO_4$ is associated with agranulocytosis or aplastic anemia, hence must be given < 1g/day and not more than 30 days. Lithium along with an ATD

may also be given in cases of severe thyrotoxicosis for expedited recovery. Risk factors for severe thyrotoxicosis includes more than 23 months on amiodarone and thyroxine > 50 % above the upper limit of normal. RAI treatment can be considered if the radioiodine uptake is high. Possibility of overlap with AIT2 must be considered if there is worsening of the thyrotoxicosis after initial control of the disease. [xc,xci,xcii]

AIT 2 is a result of release of the preformed thyroid hormone due destruction of the thyroid tissue due to the toxic effect of amiodarone. AIT 2 may appear around 30 months after starting amiodarone. AIT 2 continues until the thyroid hormones depleted which occurs in 1-3 months. The ultrasonogram shows a normal or small gland and the T4/T3 ratio is usually >4. Antibodies are usually absent in AIT 2.[xc,xci] Type 2 AIT is treated with glucocorticoids for anti-inflammatory and membrane stabilizing effects. Prednisolone can be given in the initial dose of 0.5 to 0.7 mg/kg body weight/day. Treatment is tapered and continued for three months. If worsening of the thyrotoxicosis during tapering of the treatment then the dose of Prednisolone should be increased. Anti thyroid drugs are not useful since the thyrotoxicosis is due to preformed thyroid hormones. After thyrotoxicosis resolution, hypothyroidism can develop which require thyroid hormone replacement therapy. Lithium may also benefit patients with AIT 2. Patients who do not respond to medical management should consider total thyroidectomy under careful cardiovascular monitoring.[xc,xci,xcii]

S. No.	Key Summary Point
28.	Thyroiditis can be subacute, painless, acute, post-partum or drug induced. Diagnosis can be done by clinical history, physical examination, biochemical evaluation and radioactive iodine uptake. Subacute and acute thyroiditis can be managed with the help of beta-blockers, NSAIDs, and, in some cases, corticosteroids. Symptomatic postpartum thyroiditis should be managed with a short course of Beta-blockers.
29.	Amiodarone induced thyroiditis can be identified by RAIU, T4/T3 ratio, Echo color doppler. High dose ATD (carbimazole 20-60 mg/day) for 6 to 18 months is indicated in AIT type 1. Corticosteroids is indicated in AIT type 2.

5. Thyroid Storm[i,ii,xciv]

Thyroid storm or thyrotoxic crisis is life-threatening condition with high morbidity and mortality which requires a prompt diagnosis and treatment. A decompensation across multiple organ systems occur which can manifest as altered consciousness, cardiac complications such as heart failure, diarrhea, jaundice and high fever. Diagnostic criteria in patients who have been diagnosed as severe Graves' hyperthyroidism includes tachycardia, arrythmia, congestive heart failure, hyperpyrexia, agitation, delirium, psychosis, stupor, coma, diarrhea, vomiting, nausea, hepatic failure. Such patients may also have an identified precipitant.

There can be several precipitating factors which include

- Stopping anti-thyroid drugs abruptly
- Thyroid or non-thyroid surgery
- Trauma
- Acute disease conditions such as diabetic ketoacidosis, acute myocardial infection, cardiac failure, cardiovascular accidents, stroke, traumatic brain injury and infections such as Covid-19
- Use of iodinated contrast medium
- Hyperemesis gravidarum or after Parturition
- Burns
- Radioiodine therapy
- Drug side effects such as amiodarone

Burch-Wartofsky Point Scale (BWPS)

The Burch-Wartofsky Point Scale system measures the severity of the thyroid storm. A total score of ≥45 indicates thyroid storm, 25-44 as impending thyroid storm and <25 scores indicates that thyroid storm is unlikely.

In 1993, the following scoring system for the diagnosis of thyroid storm was introduced:

- Temperature: 5 points per 1 F above 99 F (maximum 30 points)
- CNS dysfunction: 10 points for mild (agitation), 20 for moderate (delirium, psychosis, or extreme lethargy), and 30 for severe (seizure or coma)

- Tachycardia: 5 (99-109), 10 (110 -119), 15 (120 -129), 20 (130 -139) and 25 (greater than 140)
- Presence of atrial fibrillation:10
- Heart failure: 5 for mild (pedal edema), 10 for moderate (bi-basilar rales), 15 for severe (pulmonary edema)
- GI dysfunction: 10 for moderate (diarrhea, nausea/vomiting, or abdominal pain) and 20 for severe (unexplained jaundice)
- Presence of Precipitating factor: 10 points

An early and aggressive treatment is required to reduce mortality. A multimodal treatment approach is required for thyroid storm. General management includes oxygen and cardiac monitoring. For pyrexia, external cooling or acetaminophen 325 -650 Per oral (PO) or Per rectal (PR) can be given. Intravenous isotonic saline (or dextrose containing isotonic saline can be used if low blood glucose present)

Carbimazole 40 to 60 mg per oral as loading dose can be given followed by 5-20 mg daily as maintenance dose for inhibition of new TH synthesis. Methimazole, 40 mg orally as initial loading dose and maintenance dose 25 mg every 4 hours. Total daily dose: 120 mg/day. If given PR, 40 mg should be crushed in aqueous solution. PTU, a loading dose of 600–1,000 mg given PO followed by 200–250 mg every 4 h. Total daily dose: 1,200–1,500 mg/day.

Intravenous MMI 40 mg 8 hourly or PTU 400 mg 8 hourly to reduce thyroid hormone synthesis may be required.

To reduce the thyroid hormone release Iodine is required. In order to block the peripheral conversion of T4 to T3, glucocorticoid, PTU, propranolol and iodinated radio contrast is required. Intravenous glucocorticoids such as i.v. methylpredinisolone 50 mg or hydrocortisone 100 mg IV every 8 hours or dexamethasone 2 mg every 6 hours can be started. Beta-blockers to control the increased sympathetic tone such as propranolol 40 to 80 mg every 4-6 hours or short-acting beta-blocker esmolol at a loading dose of 250 mcg/kg to 500 mcg/kg followed by 50 mcg/kg to -100 mcg/kg/minute in an ICU setting can be given. Monitoring in the ICU is recommended. To reduce

enterohepatic cycling of thyroid hormone, bile acid sequestrant, cholestyramine in the doses of 4 mg four times daily is used.

PTU decreases T3 levels by 45% in the first 24 hours of treatment but may cause hepatotoxicity. Methomazole causes 10 -15% decrease in T3 levels in the first 24 hours but has less hepatotoxicity and hence PTU should be switched to methimazole after the initial stabilization.

Cause of death from thyroid storm is due to multi organ failure, heart and respiratory failure, arrythmia, gastrointestinal perforation, sepsis, disseminated intravascular coagulation, and hypoxic brain syndrome.

S.No.	Key Summary Point
30.	The Burch-Wartofsky Point Scale system measures the severity of the thyroid storm. General management includes oxygen, cardiac monitoring, pyrexia management and Intravenous fluids. High dose antithyroid drugs, iodine, corticosteroids and beta-blockers are given to manage the thyrotoxicosis. ICU monitoring is recommended.

6. Clinical Considerations for women of childbearing potential group:[xvi]

- Women in the childbearing potential group and who develop hyperthyroidism should receive proper counselling and need to be informed regarding the impact of the disease and its management on pregnancy with special consideration on family planning. It is recommended that pregnancy test is done within the first days of a missed or an unusually light menstrual period, and contact of physician within 24 hours if pregnancy is positive.
- The condition of hyperthyroidism itself as well as the treatment for hyperthyroidism lead to untoward consequences in pregnancy and fetal outcome; therefore women should reach euthyroid state before considering pregnancy. Two TFT test within an interval of atleast 1 month and without therapy change is used to demonstrate euthyroidism.
- Definitive therapy of surgery and RAI should be considered in GD patients who required high dose of ATD to become euthyroid. Thyroidectomy results in the decrease or disappearance of circulating TRAb. In case of RAI, there is an increase of transient TRAb and pregnancy must be considered in >6 months following RAI treatment, provided normalization of thyroid

hormone levels. TRAb levels must be measured using sensitive assay during the first trimester and, if elevated levels are found there should be retesting at 18-22 weeks of gestation. If TRAb levels are raised at 18-22 weeks of gestation, TRAb should be retested at late pregnancy at week 30 to 34 in order to investigate need for neonatal monitoring.

6.1 Hyperthyroidism in Pregnancy and Lactation

According to Kumar et al 2023 study in Punjab, prevalence of thyroid disorders in 300 pregnant women were identified via TSH screening and if TSH was found abnormal, further T3 and T4 testing was done. Hyperthyroidism was found in 7(2.3%) of pregnancies. The main complication associated with hyperthyroidism was abortion found in 5(71.4%) of hyperthyroid pregnancies. [xcv]

Overt hyperthyroidism in pregnancy is also diagnosed with the help of thyroid function test with TSH <0.1mIU/L and thyroid hormones (free T4 and free T3) that are above the reference ranges for pregnancy. In cases of suspected pregnancy with hyperthyroidism, it is necessary to distinguish between Graves' disease and cases of gestational transient thyrotoxicosis such as hyperemesis gravidarum.[xcvi,xcvii]

In preparation for pregnancy, the maternal thyroid gland undergoes several physiological alterations. Gestational transient thyrotoxicosis (GTT) is a condition where hCG produced by the placenta induces the TSH receptor to produce thyroid hormones T3 and T4. Compared to a non-pregnant woman, the serum concentration of TSH is also reduced. GTT presents with symptoms similar to GD such as anxiety, tremors, palpitations and heat intolerance. In conditions with exaggerated hCG production, such as in trophoblastic disease, hyperemesis gravidarum or multiple pregnancies, the GTT symptoms can be severe. [xcviii, xcix, c]

Often, the diagnosis of hyperthyroidism can remain elusive due to the fluctuating nature of the thyroid hormones. It is necessary to distinguish GTT from GD. GTT is a transient condition and mild in nature, and therefore does not require treatment with ATD. Graves' disease is associated with maternal and fetal adverse outcomes and hence, needs careful management with appropriate ATDs and monitoring. TRAbs are of special significance in such cases since positive TRAb can help confirm Graves' disease and can differentiate from the gestational transient thyrotoxicosis. Presence of Graves' orbitopathy, goiter and previous GH are also indicative of the diagnosis of Graves' disease. [xvi,xcviii,xcix,ci] It is important to elicit a history of Graves' disease in pregnant women

who have undergone Radioiodine ablation treatment or surgery, since the circulating TRAb may persist and lead to fetal thyrotoxicosis. In euthyroid pregnant women with history of Graves' disease who achieved remission with ATDs (with intact thyroid) and currently not on treatment, TRAb testing is not indicated.[xvi]

Diagnosed gestational transient thyrotoxicosis as well as subclinical hyperthyroidism can be managed with observation without treatment with continuous monitoring of thyroid function test every 4-6 weeks. Untreated overt hyperthyroidism can lead to adverse maternal outcome and increased fetal loss, therefore treatment with antithyroid drugs is necessary in spite of their ability to cause teratogenicity. [xvi,c,ci]

Propylthiouracil is preferred in the first trimester due to the association of carbimazole and methimazole with choanal atresia, aplasia cutis, abdominal wall defects, esophageal atresia, eye abnormalities, urinary tract abnormalities and defects in circulation. After the completion of organogenesis in the first trimester, the patient can be transitioned to carbimazole or methimazole since propylthiouracil is associated with hepatotoxicity. [xcviii] In case of intolerance or allergy to propylthiouracil, the patient may be given carbimazole or methimazole. The lowest possible anti-thyroid dose for maintaining effectiveness must be used.[xcvi,cii]

Maternal TRAbs are IgG protein type which can cross placenta and stimulate the fetal thyroid gland causing fetal hyperthyroidism. ATDs can cross placenta and control the fetal hyperthyroidism. A caution must be undertaken to prevent fetal hypothyroidism while the patient is on ATD. Therefore, the goal of treatment is to use the lowest ATD dose in order to target the TSH to a value that is slightly lower than the reference range and a T4 that is on the higher end of the normal reference range. A maternal state of mild hyperthyroidism with careful monitoring to prevent fetal hypothyroidism should be achieved. If it is observed that the TSH is normalized Beta-blockers such as propranolol may provide symptomatic relief. Propanolol is preferred over atenolol due to decreased birth weight being associated with atenolol. Beta-blockers must always be given for a short term to control the symptoms of hyperthyroidism. Long term beta-blockers may increase the risk of intrauterine fetal growth retardation. Iodides are contraindicated due to risk of fetal goiter. [xvi,xcix]

In cases of Graves' Disease treated with thyroidectomy or RAI, maternal euthyroidism combined with positive TRAb test can be seen in pregnancy. In such cases, TRAb evaluation must be done

in the first trimester along with the thyroid function test. If the TRAb levels are elevated at first trimester evaluation, a reassessment must be done at 18 to 22 weeks of gestation. This may lead to fetal thyrotoxicosis and can be detected clinically fetal tachycardia (Fetal heart rate>160). Re-evaluation should occur be done in 2 weeks with the help of fetal ultrasound (improvement in fetal heart rate and resolution of goiter) In such cases block-replace regimen of antithyroid drugs can treat fetal thyrotoxicosis since ATDs can cross placenta while levothyroxine which does not cross placenta can maintain maternal euthyroidism. In patients with raised TRAb levels at 18-22 weeks, the TRAb levels need to be reassessed at 30 to 34 weeks to guide clinical decision related to neonates.[xvi]

In pregnant women with overt hyperthyroidism and where the diagnosis is determined to be multinodular goiter or toxic adenoma, anti-thyroid drugs may be given. Adequate care must be undertaken to prevent fetal hypothyroidism in such cases since unlike Graves' disease, TRAb are not present to stimulate the thyroid gland.[xvi]

In women developing thyrotoxicosis in the postpartum period, there is need to distinguish postpartum destructive thyroiditis and postpartum Graves' disease. Postpartum thyroiditis follows the triphasic course: thyrotoxicosis emerging at 1-6 months postpartum, followed by hypothyroidism and euthyroidism at 9 to 12 months. Symptomatic postpartum thyroiditis should be managed with a short course of beta-blockers. Postpartum GD emerges at 3 to 12 months after delivery and may be characterized by pronounced goiter, thyroid bruit and Graves' ophthalmopathy. While TRAb may be present in patients with both postpartum thyroiditis and postpartum Graves' disease, higher TRAb levels may be present in women with postpartum GD. T3 to T4 ratio is high in Graves' disease relative to destructive thyroiditis. Thyroid ultrasonography may be adopted to distinguish Graves' disease and thyroiditis. Radioactive scintigraphy scans to diagnose the cause of postpartum thyrotoxicosis should be avoided to prevent disruption in breastfeeding as well as to prevent exposure of the breast to radiation. [xvi]

According to the 2016 American Thyroid Association guidelines, the following practice points may be undertaken in a hyperthyroid pregnancy [xvi]

- Carbimazole and methimazole is associated with increased risk of congenital association.[ciii]

- Patient can switch to propylthiouracil before conceiving or as soon as pregnancy is diagnosed especially in patients with recurrent or worsening hyperthyroidism
- ATD can be withdrawn in some appropriate patient candidates in whom relapse risk is low (severity of disease, ATD treatment duration, TRAb and TFT test results) as soon as pregnancy is detected; however, Thyroid function must be monitored weekly in the first trimester and then monthly
- After first trimester, patient can be switched to carbimazole or methimazole in the second trimester or can be continued for the rest of the pregnancy.
- Lowest possible dose of ATD should be used during pregnancy to keep maternal thyroid hormone levels at or slightly above the reference range of total T4 and T3 levels in pregnancy and TSH below reference range for pregnancy. Free T4 levels should be above upper limit of trimester reference range.
- Monitoring should be undertaken at least monthly interval to allow for the titration of the ATD dose
- Patients can consider definitive treatment before becoming pregnant

- Thyroidectomy is relatively contraindicated in pregnancy and is utilized if ATDs are contraindicated; if this approach is used, surgery should be conducted in the second trimester. Surgery may also be indicated if ATDs fail to control hyperthyroidism at high doses. (propylthiouracil 300 mg/day; methimazole or carbimazole 40 mg/day)[civ,cv]
- If the cause of hyperthyroidism is not ascertained, TRAb testing must be done

Management of Hyperthyroidism in Lactation

Use of Anti-Thyroid Drug in lactation[civ,cv]

- Carbimazole has been studied in doses of 30 mg daily or 50 mg weekly in few mothers of breastfed infants and has not shown any adverse effects.
- Methimazole in doses up to 20 mg daily in lactating mother has not been seen to affect the thyroid function or intellectual development of breastfed infants
- To minimize the infant dose, methimazole can be taken right after nursing and waiting for 3 to 4 hours before nursing.

- Beta-blockers such as propranolol and metoprolol is secreted in the breast milk in very low amounts and can be used for symptomatic control of thyrotoxicosis.
- Routine pediatric health monitoring must be undertaken for infants for growth and development
- Routine thyroid function test is not recommended for children
- Suspicion of drug-induced dyscrasia should be confirmed with the monitoring of infant's complete blood count and differential blood count

S. No	Key Summary Point
31.	Proper counselling is required in women with hyperthyroidism since the condition of hyperthyroidism itself as well as the treatment for hyperthyroidism lead to untoward consequences in pregnancy and fetal outcome.
32.	Women should reach euthyroid state before considering pregnancy. Two TFT test within an interval of at least 1 month and without therapy change is used to demonstrate euthyroidism
33.	Definitive therapy of surgery and RAI should be considered in women with hyperthyroidism desirous of pregnancy who required high dose of ATD to become euthyroid. In case of RAI, there is an increase of transient TRAb, and pregnancy must be considered in >6 months following RAI treatment, provided normalization of thyroid hormone levels.
34.	In pregnancy the cause of hyperthyroidism is not ascertained, TRAb testing must be done
35.	Once pregnancy is confirmed, hyperthyroid patient can switch to PTU before conceiving or as soon as pregnancy is diagnosed. After first trimester, patient can be switched to carbimazole or methimazole in the second trimester or can be continued for the rest of the pregnancy
36.	Thyroidectomy is relatively contraindicated in pregnancy and is utilized if ATDs are contraindicated; if this approach is used, surgery should be conducted in the second trimester
37.	Antithyroid may be given in lactating mothers. To minimize the infant dose, anti-thyroid drug can be taken right after nursing and waiting for 3 to 4 hours before nursing. Routine pediatric health monitoring must be undertaken for infants for

	growth and development. Suspicion of drug-induced dyscrasia should be confirmed with the monitoring of infant's complete blood count and differential blood count

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