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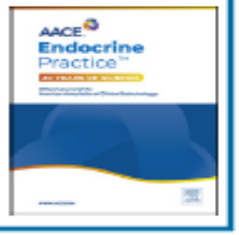

Review Article

Management Aspects of Medical Therapy in Graves Disease

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Mini-Review

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Treatment of Hyperthyroidism in Graves' Disease Complicated by Thyroid Eye Disease

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Seminar

Hyperthyroidism

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Thyrotoxicosis causes a variety of symptoms and adverse health outcomes. Hyperthyroidism refers to increased thyroid hormone synthesis and secretion, most commonly from Graves' disease or toxic nodular goitre, whereas thyroiditis (typically autoimmune, viral, or drug induced) causes thyrotoxicosis without hyperthyroidism. The diagnosis is based on suppressed serum concentrations of thyroid-stimulating hormone (TSH), accompanied by free thyroxine and total or free tri-iodothyronine concentrations, which are raised (overt hyperthyroidism) or within range (subclinical hyperthyroidism). The underlying cause is determined by clinical assessment, detection of TSH-receptor antibodies and, if necessary, radionuclide thyroid scintigraphy. Treatment options for hyperthyroidism include antithyroid drugs, radioactive iodine, and thyroidectomy, whereas thyroiditis is managed symptomatically or with glucocorticoid therapy. In Graves' disease, first-line treatment is a 12–18-month course of antithyroid drugs, whereas for goitre, radioactive iodine or surgery are preferred for toxic nodules or goitres. Evidence also supports long-term treatment with antithyroid drugs as an option for patients with Graves' disease and toxic nodular goitre.

Epidemiology

- In iodine-sufficient regions, overt and subclinical hyperthyroidism each affect 0·5%, with a combined incidence of 50 /100 000 per year (GD).
- In iodine-deficient areas, prevalence of hyperthyroidism is higher: up to 10–15% for overt and subclinical hyperthyroidism combined (toxic MNG)
- Correction of iodine deficiency can result in a transient increase in the incidence of hyperthyroidism, followed by a gradual decrease to levels recorded in iodine-sufficient regions.
- **GD**
  - prevalence of GD is 1% to 2% worldwide, with a lifetime risk of 3% in women and 0.5% in men
  - incidence in iodine-sufficient regions is 20–30 /100 000 per year
  - peak in the third to fifth decades of life
  - F/M:5–6/1.
  - **toxic nodular goiter**
  - Incidence :3–6 / 100 000 per year in iodine-sufficient areas to 20–40 /100 000 per year in iodine-deficient areas
  - >=50 years
  - more common in females than males

	Alternative names	Pathogenesis	Clinical pointers
Thyrotoxicosis with hyperthyroidism	--	Increased thyroid hormone synthesis and secretion by the thyroid	--
Graves' disease	Basedow disease, diffuse toxic goitre	Stimulating antibodies to TSH receptor	Diffuse goitre, thyroid bruit (pathognomonic), ophthalmopathy
Toxic nodular goitre	Toxic adenoma, autonomous thyroid adenoma, Plummer's disease	Single or multiple autonomous adenomas, somatic activating mutations in TSH receptor	Asymmetric, irregular goitre; visible or palpable nodule(s)
Gestational hyperthyroidism	--	High values of hCG stimulating TSH receptor	First trimester of pregnancy, hyperemesis gravidarum, multiple pregnancy
Gestational trophoblastic disease	--	As for gestational hyperthyroidism	Hydatidiform mole, trophoblastic tumour
Iodine-induced hyperthyroidism	Jod-Basedow phenomenon	Excess iodine substrate (usually in gland with underlying autonomous function)	History of excessive iodine or kelp ingestion, radiographic contrast exposure
Type 1 amiodarone-induced thyrotoxicosis	--	As for iodine-induced hyperthyroidism	Amiodarone treatment, underlying thyroid disease
Thyrotropinoma	TSHoma	TSH secretion by pituitary adenoma	Pituitary tumour, elevated free T4 and (free)T3 with unsuppressed TSH
Thyroid hormone resistance β*	--	Mutation in *TRb* gene	Attention deficit hyperactivity disorder, tachycardia, diffuse goitre
Familial non-autoimmune hyperthyroidism	--	Germline activating mutation in TSH receptor	--

Thyrotoxicosis without hyperthyroidism	..	Increased circulating thyroid hormones without increased synthesis of thyroid hormone by the thyroid	..
Thyroiditis	..	Inflammation leading to release of stored thyroid hormone from thyroid follicles	..
Lymphocytic thyroiditis	Silent thyroiditis, painless thyroiditis, autoimmune thyroiditis, includes post-partum thyroiditis	Autoimmune thyroiditis	Positive TPOAb, post-partum presentation
Subacute thyroiditis	De Quervain thyroiditis, granulomatous thyroiditis, viral or post-viral thyroiditis, painful thyroiditis	Viral or post-viral inflammation	Preceding viral illness; painful, tender thyroid; negative TPOAb
Other forms of thyroiditis	..	..	..
Drug-induced	..	Various	..
Traumatic	..	Trauma, manipulation, palpation	..
Radiation-induced	..	Radiation thyroiditis	..
Bacterial, fungal	..	Bacterial or fungal infection	..
Exogenous thyroid hormone	..	Excessive thyroid hormone use (iatrogenic or factitious)	..
Struma ovarii	..	Ectopic thyroid hormone secretion from ovarian teratoma	Pelvic mass; very rare

TSH=thyroid-stimulating hormone. T4=thyroxine. T3=tri-iodothyronine. TPOAb=thyroid peroxidase antibodies. *Not part of classic hyperthyroidism: mixed hyperthyroid and hypothyroid state dependent on target tissue.

Table 1: Causes of thyrotoxicosis

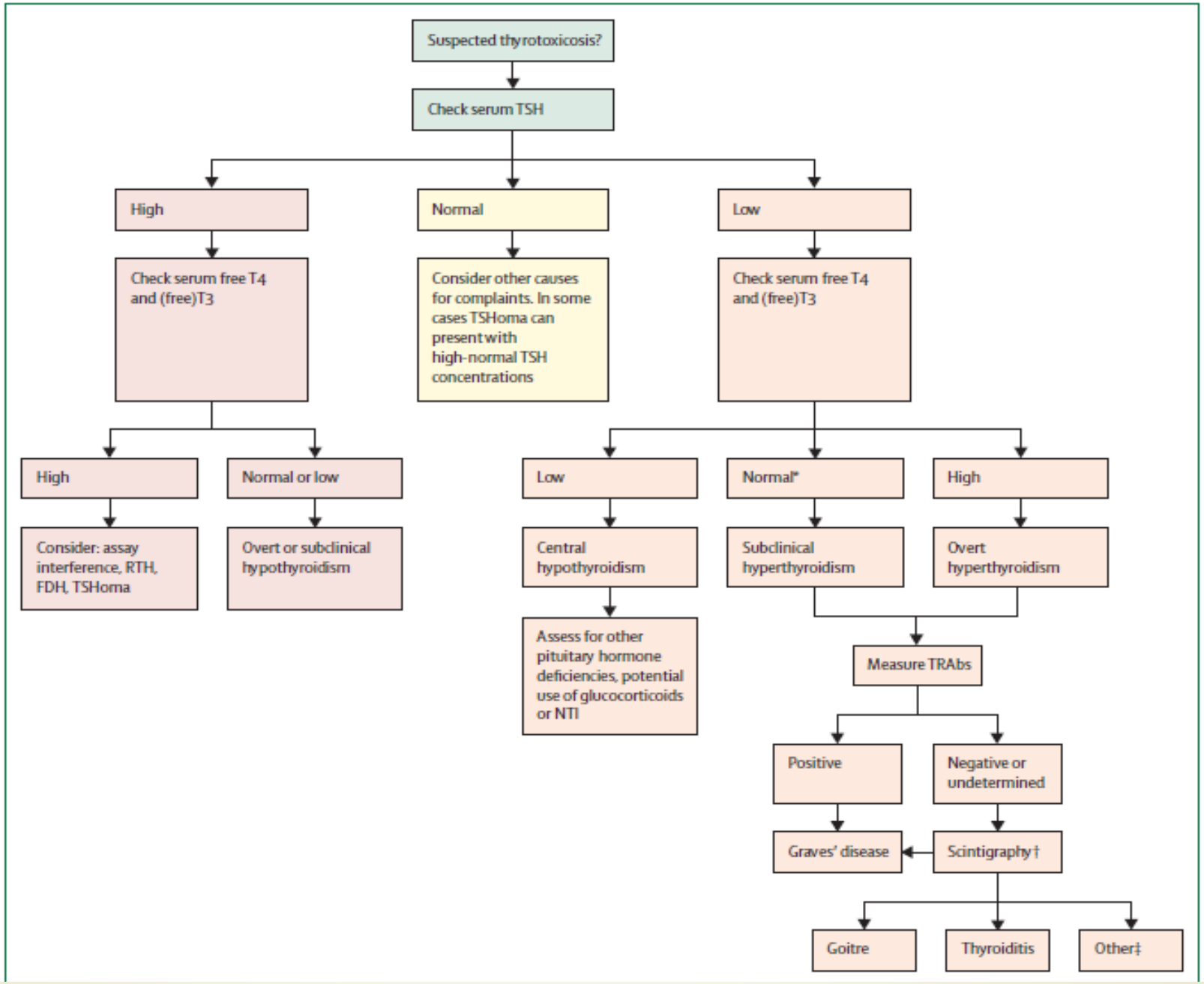
	Symptoms*	Signs*
General	Nervousness, insomnia, fatigue	Anxiety, restlessness
Skin	Diaphoresis, thinning hair	Warm, moist skin, onycholysis, alopecia†, acropachy†, urticaria*, vitiligo*
Eyes	Dry eye, eye protrusion, diplopia, photophobia	Proptosis†, conjunctival injection†, chemosis†, decreased visual acuity†, lid lag†
Neck	Anterior neck swelling, dysphagia	Goitre
Cardiovascular	Palpitations, dyspnoea on exertion, chest pain	Tachycardia, tachyarrhythmia, congestive heart failure‡
Gastrointestinal	Hyperdefecation, diarrhoea	Abnormal liver function tests
Metabolic	Hyperphagia, weight loss, heat sensitivity	Cachexia, fever‡
Neuromuscular	Muscle weakness, paralysis§	Hyper-reflexia, proximal muscle weakness, muscle wasting, hypokalaemic periodic paralysis§
Skeletal	--	Low bone mass and fractures, hypercalcaemia, hypercalciuria
Neurological	Tremor	Tremor, stupor‡, coma‡, choreoathetosis§
Reproductive/sexual	Oligo-amenorrhoea, decreased fertility in women, decreased libido in men	Gynecomastia
Haemopoietic	--	Leukopenia†, normochromic normocytic anaemia, splenomegaly†, thymic enlargement†
Psychiatric/cognitive	Emotional lability, poor concentration, irritability	Depression, psychosis, irrational behaviour

*Signs and symptoms of hyperthyroidism are less specific or might be absent in patients of older age. †Findings seen in Graves' disease. ‡Findings seen in thyroid storm. §References for rare findings are provided in the appendix.

Table 2: **Signs and symptoms of hyperthyroidism, by system**

Clinical presentation and complications

- Some patients have several complaints that seem out of proportion to their apparent modest biochemical hyperthyroidism, whereas others are oligo symptomatic despite very high serum hormone concentrations. Age is one factor, with older individuals having few hyperthyroid symptoms.
- biochemical findings in hyperthyroidism are microcytic anemia, thrombocytopenia, bilirubinemia, high transaminases, hypercalcemia , high ALKP , low- LDL and HDL
- in older people : unexplained weight loss, AF or atrial flutter, palpitations, altered mood
- GO: prevalence of 25–40% among GD.
- Untreated hyperthyroidism is associated with various adverse outcomes, especially in older individuals.
- Cardiovascular adverse events are most important, especially AF leading to HF and embolic stroke.
- Fractures are more common, especially in postmenopausal women
- Overall quality of life is diminished in individuals with untreated hyperthyroidism especially if they have concomitant GO


Suspected thyrotoxicosis?
Check serum TSH
High
Normal
Low
Check serum free T4 and (free)T3
Consider other causes for complaints. In some cases TSHoma can present with high-normal TSH concentrations
Check serum free T4 and (free)T3
High
Normal or low
Low
Normal*
High
Consider: assay interference, RTH, FDH, TSHoma
Overt or subclinical hypothyroidism
Central hypothyroidism
Subclinical hyperthyroidism
Overt hyperthyroidism
Assess for other pituitary hormone deficiencies, potential use of glucocorticoids or NTI
Measure TRAbs
Positive
Negative or undetermined
Graves' disease
Scintigraphy†
Goitre
Thyroiditis
Other‡

Diagnosis of thyrotoxicosis

- Overt thyrotoxicosis is characterized by serum TSH, usually less than 0 ▪ 01 mU/L.
- T3 thyrotoxicosis is common in patients with milder disease or early in the course of disease.
- Measurement of the freeT4 is preferred over the measurement of total T4, because it reflects the freely available hormone
- Because of limitations of current free T3 assays, either total or free T3 can be measured.
- A FT3/FT4 ratio >0.3 or total T3/T4 ratio of >20 ng/mg may suggest GD.
- There are 2 available methods for detecting antibodies against TSH receptors:
  - **TBI** assay: TBI assays are more commonly referred to as TRAb TBI assays have evolved over time and the current third-generation binding assays are automated and have improved sensitivity and specificity of up to 97% and 99% for diagnosing GD.
  - **TSI** is a subtype of TRAb, TSI, is a cell-based bioassay that detects stimulating immunoglobulins and, is more sensitive.
  - assays do not differentiate between stimulating, inhibiting, or neutral AbsTRAb measurement can particularly be useful in

- Analytical interference from circulating heterophilic AB can affect TSH measurements resulting in discordant thyroid function tests (eg, increased thyroid hormones with unsuppressed TSH).
- In assays using streptavidin-biotin detection systems, ingestion of biotin supplements by patients can cause concomitantly falsely raised thyroid hormone and falsely suppressed TSH
- In patients in whom the cause of thyrotoxicosis is not readily apparent, scintigraphy and radioisotope uptake are useful to determine the cause.
- Radioisotopes of iodine (123I and 131I) or ^{99}-technetium are administered
- In some centers , assessment of thyroidal vascularity by ultrasound with colourflow Doppler or elastography is used in preference to thyroid scintigraphy to differentiate between GD and other causes of thyrotoxicosis
- Images are not routinely necessary for diagnosing GD but can be helpful.

Usefulness of TRAb in Certain Scenarios

TRAb measurement can be useful in the following scenarios:
• Hyperthyroidism during pregnancy • Patients with possible TED without biochemical hyperthyroidism • Recent iodine load where thyroid uptake scan cannot be reliable, eg, recent amiodarone use, recent imaging studies with iodinated contrast • To determine the prognosis for remission in those treated with ATD

Abbreviations: ATD = antithyroid drugs; TED = thyroid eye disease.

Graves' disease

- high degree of heritability:60–80%.
- Similar to other autoimmune diseases, skewed X chromosome inactivation is probably an important contributor to the female predominance.
- meta-analysis between 1980 and 2017,shown GD phenotype at diagnosis seems to be milder than in the past

TABLE 10.1 Phenotypes of Graves Disease and Their Estimated Incidence Rates

Phenotype	% Affected	Cases/Million/Year
All	100	350
Graves hyperthyroidism	90–95	325
Goiter	50	175
Graves orbitopathy	30	105
Severe orbitopathy	5	17
Hypothyroidism + orbitopathy	5	17
Graves dermopathy	0.5	4
Neonatal hyperthyroidism	0.2	1.0
Fetal hyperthyroidism	0.1	0.5
Acropachy	0.1	0.5

Table 1

Risk Factors Associated With Graves Disease

Nonmodifiable[a]	Modifiable/environmental factors
Genetic predisposition: HLA-DR3, CTLA-4, TSH-R	Smoking
Estrogen exposure/female sex	Iodine exposure
Postpartum	Selenium deficiency
	Vitamin D deficiency
	Viral infections[b]
	Agent Orange exposure
	HCV-related mixed cryoglobulinemia
	Medications—ICI, alemtuzumab, HAART in HIV

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte associated protein 4; HAART = highly active antiretroviral therapy; HLA = human leukocyte antigen; ICI = immune checkpoint inhibitors; TSH-R = thyroid-stimulating hormone receptor.

[a] Nonmodifiable risk factors are present in majority of patients.

[b] Viruses studied include Epstein-Barr virus, parvovirus-B19, foamy viruses, hepatitis C virus.

Thyroiditis

- Thyrotoxicosis is transient and self-limited, resolving after 1–4 months
- **Lymphocytic thyroiditis** (silent thyroiditis)
  - Th1 and Th17 immune responses predominate, with lymphocytic infiltration of the thyroid, lymphoid follicle formation, and thyroid follicular atrophy.
  - Most, but not all, have circulating anti TPO or anti TG, or both.
  - Post-partum thyroiditis is a subtype (5% of women in the first year post partum), about half of whom have thyrotoxicosis.
- **Sub acute thyroiditis** :
- fever and systemic inflammatory symptoms
- caused by viral infection of the thyroid or a post viral inflammatory state in predisposed individuals (HLA-B35 and HLA-B67 status)
- granulomatous change, giant cell formation, and a mixed monocytic and lymphocytic inter follicular infiltrate.
- incidence of 2–5 /100 000 per year,
- F/M:3–7:1.
- several viruses including mumps, echoviruses, coxsackie viruses, and SARS-CoV-2.
- many case reports of sub acute thyroiditis after COVID-19 vaccination , the association could be coincidental.

Thyroiditis

Drug-induced thyroiditis

- Checkpoint:
  - thyroiditis occurs in 10% of treated patients
  - higher rates in pre-existing thyroid autoimmunity.
- Thyroiditis is more common with programmed cell death-1 (PD-1) inhibitors or combination therapy than with PD-L1 inhibitor or CTLA-4inhibitor monotherapy.
- Thyrotoxicosis occurs in 3–5% of patients treated with interferon-a.

Panel: Drugs associated with thyroiditis and thyrotoxicosis

- Immune checkpoint inhibitors
  - PD-1 inhibitors: pembrolizumab, nivolumab, cemiplimab, dostarlimab
  - PD-L1 inhibitors: atezolizumab, avelumab, durvalumab
  - CTLA-4 inhibitors: ipilumamb, tremelimumab
- Cytokines
  - Interferon-α, interleukin-2
- Tyrosine kinase inhibitors
  - Sunitinib, sorafenib
- Lithium
- Amiodarone
  - Type 2 amiodarone-induced thyrotoxicosis
- Alemtuzumab (also associated with Graves' disease)

Toxic nodular goiter

- Thyroid nodules are common in setting of iodine deficiency
- chronic stimulatory effect on the thyroid, resulting in diffuse or nodular goiter
- Genetic factors, female sex, and smoking contribute to nodule development.
- Functional autonomy develops in about 5% of thyroid nodules, either as solitary toxic adenomas or MNG.

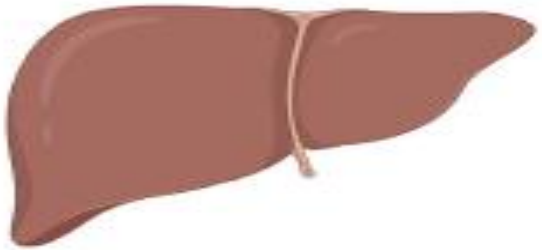
Treatment

- most common options are ATD,RAI, and thyroidectomy.
- **toxic adenoma or MNG**
  - RAI and surgery the preferred options.
  - long-term, low-dose ATD is effective, especially in older patients or those who are poor candidates for RAI treatment or surgery.
- **GD**
  - all three treatment options are effective
  - ATD may be the patient-preferred approach.
  - A cohort study of 1186 patients with GD followed up for up to 10 years after with RAI reported lower quality of life .findings from an earlier, showed no difference.
  - Clinicians in Europe and the Asia-Pacific region prefer ATD as first-line treatment. In the USA, treatment choices have shifted in favor of ATD over RAI in the past two decades.
  - During the COVID-19 pandemic, non-urgent surgery and RAI treatment were curtailed in many countries, leading to a further shift towards the use of ATD

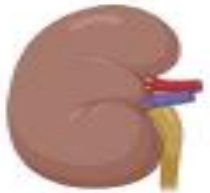
Antithyroid drugs: Pharmacokinetics and mechanism of action

- Inhibit TPO mediated iodination of tyrosine residues in thyroglobulin
- Inhibit the coupling of the iodotyrosine residues forming T3 & T4
- Lower thyroid autoimmunity (direct or indirect effect)
- PTU prevents the conversion of T4 to T3 within the thyroid and peripheral tissue by inhibiting Type 1 deiodinase

- Orally absorbed
- Peak within 1-2 hrs
- MMI Longer duration of action than PTU [allows for once daily dose]



- Liver metabolism
- PTU is mostly bound to albumin, MMI is free in serum



- Urinary excretion metabolites
- No dose adjustments necessary in renal failure

- Transfer across placenta & breast milk

Fig. 1. Antithyroid drugs: pharmacokinetics and mechanism of action. *MMI* – methimazole; *PTU* – propylthiouracil; T4 – thyroxine; TPO – thyroid peroxidase; T3 – triiodothyronine.

Table 2

Initial Medical Management of Graves Disease

Medication class	Dosage and frequency	Considerations	Side effects
Beta-blockers			
Propranolol	10-40 mg 3-4 times a day	Nonselective beta-blockade, preferred in pregnancy May block T4 to T3 conversion	Cardiac: heart failure exacerbation, bradycardia Noncardiac: bronchoconstriction, depression, fatigue, sexual dysfunction
Metoprolol	25-50 mg 2-3 times a day	Beta one selective	
Atenolol	25-100 mg 1-2 times a day	Once daily dosing, better compliance, avoid in pregnancy	
Esmolol	IV pump 50-100 μg/kg/min	ICU setting in severe thyrotoxicosis or storm	
Antithyroid medications			
Methimazole	5-40 mg daily[a]	First-line Better efficacy and safety, better compliance	Minor (5%): gastrointestinal distress and pruritis Major (<0.5%): agranulocytosis and hepatotoxicity (cholestatic or hepatocellular), vasculitis, pancreatitis
Propylthiouracil	50-150 mg 3 times a day	Second-line (if unable to tolerate methimazole) Preferred in first trimester of pregnancy	

ICU = intensive care unit.

[a] Higher doses of 30-40 mg/d may be required for patients with severe hyperthyroidism or larger goiter.

ATD

- treated for 12–18 months with carbimazole and methimazole according to American and European guidelines
- they can be discontinued if TSH is normal and TRAb is negative.
- persistent high TRAb on treatment or relapse after treatment withdrawal, patients can choose carbimazole and methimazole for a further 12 months (or longer), or opt for definitive treatment
- ATD is high relapse rates (about 50%) after a single
- Evidence shows that long-term (5–10 years) or perhaps even lifelong treatment with low dose carbimazole and methimazole is a safe.
- tripterygium glycosides could enhance the effect of methimazole and prednisone in treatment of hyperthyroidism, without increasing side effects.
- meta-analysis showed combination of several regimens (including iodine, cholestyramine, and immunosuppressants) with methimazole to be efficacious in reducing free T3 and T4 values.

Treatment

- Long-term treatment with a low-dose ATD is a feasible strategy to control hyperthyroidism and avoid relapse, and seems to be safe and effective in both Graves' disease and toxic nodular goiter.

- long-term low-dose ATD might become an appealing option in GD
- definitive therapy or starting long-term ATD therapy In patients:
  - low chance of remission smoker ,have high TRAb titres) or
  - relapse would be detrimental because of underlying other abnormalities (eg, heart disease)
  - Evidence suggests an increase in remission rate with every additional year of ATD therapy.
- TED may occur in patients with euthyroid/hypothyroid chronic autoimmune thyroiditis (6-7% of cases), the large majority of patients have GD.
- TED development may precede hyperthyroidism or follow it, but in general its onset is temporally related to the onset of hyperthyroidism and occurs within 18 months from the onset of hyperthyroidism in 85% of cases

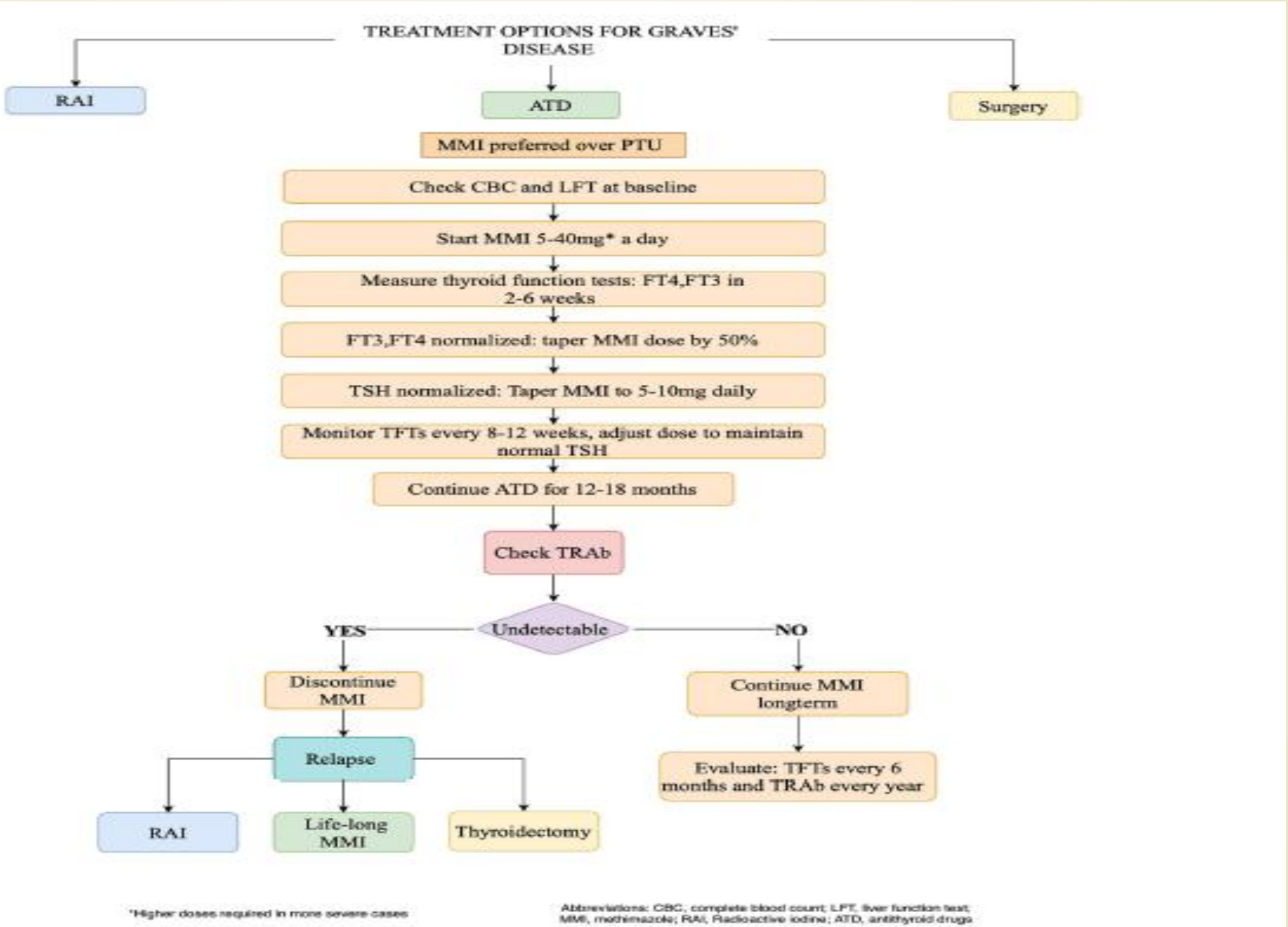


Fig. 2. Proposed algorithm for initial and long-term medical management of Graves disease. *ATD* – antithyroid drug; *CBC* – complete blood count; *FT4* – free thyroxine; *FT3* – free triiodothyronine; *LFT* – liver function test; *MMI* – methimazole; *TFT* – thyroid function test; *TRAb* – thyrotropin receptor antibody; *TSH* – thyroid-stimulating hormone.

Predictors of Response to Antithyroid Medications

Biochemically responsive/ remission	Biochemically persistent/recurrence
• Higher frequency of hypothyroidism during treatment • Lesser degree of thyrotoxicosis • Smaller goiter • TRAb <3.0 mIU/L	Strong evidence: • TRAb >8.0 mIU/L and persistence • Goiter size/thyroid volume • Smoking • Postpartum period Possible/uncertain: • Higher maintenance dose of MMI • Graves ophthalmopathy at presentation • Higher FT4 levels • Insomnia • Male sex • Mental disorder • Use of iodized salt • Young age • Family history • GREAT score class II or GREAT+ score IV

Abbreviations: FT4 = free thyroxine; GREAT = Graves Recurrent Events After Therapy; MMI = methimazole; TRAb = thyrotropin receptor antibody.

ATD

- initial dose of ATD depends on the severity of hyperthyroidism and size of thyroid gland.
- Overtreatment resulting in hypothyroidism should be avoided, particularly in GD, because it can provoke or exacerbate thyroid eye disease.
- biochemical euthyroidism: follow-up intervals extended to 2–4 months.
- Major side-effects of ATD
  - rare
  - serious side-effects are dose related with carbimazole and methimazole, which has not been reported for PTU.
  - Agranulocytosis :
    - within the first 3 months of treatment, and can present with fever or sore throat, or both. Patients should be alerted for the occurrence of these symptoms and,
    - if agranulocytosis is confirmed, ATD should be discontinued permanently.
  - Hepatoxicity
  - cholestatic or hepatocellular
    - more severe with PTU particularly in children and in the first 3 months of therapy with cases of fatal liver failure reported. For that reason, PTU received a so called black box warning
    - increased risk of acute pancreatitis in patients given carbimazole and methimazole, although evidence for this effect is conflicting.

RAI

- first-line treatment in toxic adenoma and toxic MNG, especially for older patients with comorbidities incurring higher surgery risk.
- administered either as a fixed activity or calculated activity on the basis of thyroid size and the 24 h radioiodine uptake.
- In the first weeks after treatment, T4 and T3 concentrations can transiently increase, but ultimately hypothyroidism occurs in 50–85% of treated patients with GD
- Relief of hyperthyroidism after RAI is not achieved in roughly 10% of patients after initial treatment and depends on the underlying cause.
- RAI a definitive treatment option, but the effects are not immediate.
- reduce goiter volume up to 60% in MNG
- Carbimazole and methimazole or β blockers are typically prescribed before RAI to control hyperthyroidism and reduce risk for post-treatment exacerbation, especially in older patients and those with severe hyperthyroidism.
- ATD should be stopped a 3–7 days before ^{131}iodine administration and may be restarted 3–7 days later and continued until euthyroidism occurs.

RAI

- Side-effects :neck tenderness ,worsening of pre-existing thyroid eye disease, especially in people who smoke.
- RAI is contraindicated in GD with severe orbitopathy,
- glucocorticoid prophylaxis is recommended in:
  - mild orbitopathy
  - at risk of de-novo thyroid eye disease (smoke, with severe or unstable hyperthyroidism, and with high serum TRAb
- Untreated hypothyroidism after RAI should be avoided since this treatment can elicit or worsen thyroid eye disease.
- Other contraindications to RAI therapy
  - pregnancy (or pregnancy planned in the next 6 months)
  - breastfeeding
  - inability to adhere to radiation safety precaution
- some evidence suggests a dose-dependent positive association between RAI and solid cancer mortality; however, findings are controversial

RAI

- Achieving and maintaining euthyroidism or inducing and treating hypothyroidism appear to reverse the mortality excess seen in hyperthyroidism.
- hypothyroidism induced by RAI followed by T4 replacement reverses the increased risk of cardiovascular disease and total mortality.
- achieving euthyroidism with ATD does not necessarily reverse the increased mortality risk , because patients are not always euthyroid while receiving ATD and might relapse when treatment is stopped.
- The effect of long-term treatment with low-dose ATD on risk of cardiovascular disease and mortality is yet unknown, but could be more favorable than shorter or repeated courses.
- In autonomous benign thyroid nodules
  - RF ablation an alternative to current strategies.
  - RF ablation with a moving-shot technique showed normalization of TSH in half of patients with a low complication rate and improvement of local cervical discomfort.

Thyroidectomy

first-line treatment for

- Toxic MNG
- definitive treatment for GD, when other treatments are ineffective, not tolerated, or contraindicated (eg, RAI in severe orbitopathy)
- suspected malignant nodules
- large goiters
- concurrent primary hyperparathyroidism;
- thyroidectomy is the patient's preference.

- GD :
- total thyroidectomy preferred.
- ATD should be used to achieve euthyroidism before surgery.
- Pretreatment with Lugol's iodine or potassium iodide decreases intraoperative blood loss for patients with GD recommended

Thyroidectomy

- Toxic MNG: hemi thyroidectomy or total thyroidectomy might be appropriate depending on the number and distribution of thyroid nodules.
- Surgical complications:
  - 1–2% when undertaken by high-volume thyroid surgeons (ie, those doing >25–50 thyroidectomies/ year).
  - postoperative bleeding
  - hypocalcaemia (usually transient) due to hypoparathyroidism
  - recurrent laryngeal nerve injury

Assessment of activity

1. Spontaneous retrobulbar pain
2. Pain on attempted upward or downward gaze
3. Redness of eyelids
4. Redness of conjunctiva
5. Swelling of caruncle or plica
6. Swelling of eyelids
7. Swelling of conjunctiva (chemosis)

Table 3 Classification of severity of Graves' orbitopathy (GO).

Classification	Features
Mild GO	Patients whose features of GO have only a minor impact on daily life that have insufficient impact to justify immunomodulation or surgical treatment. They usually have one or more of the following: • minor lid retraction (<2 mm) • mild soft-tissue involvement • exophthalmos • <3 mm above normal for race and gender • no or intermittent diplopia and corneal exposure responsive to lubricants
Moderate-to-severe GO	Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have two or more of the following: • lid retraction ≥ 2 mm • moderate or severe soft-tissue involvement • exophthalmos ≥ 3 mm above normal for race and gender • inconstant or constant diplopia
Sight-threatening (very severe) GO	Patients with dysthyroid optic neuropathy and/or corneal breakdown

Thyroid Eye Disease

clinically in 30% to 40% of GD patients

- *orbital/ periocular* disease of autoimmune origin driven by activation of the TSHR and the IGF-I receptor, leading to orbital fibro adipose tissue and extraocular muscle volume expansion and mononuclear cell infiltration
- increased orbital tissue volume, the consequence of increased water binding capacity and de novo adipogenesis
- TED is more prevalent in women but more severe in older men and in asymmetric (30%) or unilateral (11%)
- modifiable risk factors for the development of TED:
  - Tobacco smoke exposure
  - uncontrolled thyroid dysfunction (both hyperthyroidism and hypothyroidism)
  - RAI thyroid ablation
  - possibly dyslipidemia

Thyroid Eye Disease

- why TED does not develop in all patients with GD, may be asymmetrical or unilateral, or presents with different severities remain unexplained.
- TED is most frequently mild and non progressive, but moderate to severe disease occurs in 10% of patients with GD
- Sight-threatening TED can result from corneal breakdown or compressive optic neuropathy, rare and emergencies
- When TED develops, an initial period of inflammation and progression (active phase) is typically followed by an inactive (stable) phase after 2 to 3 years

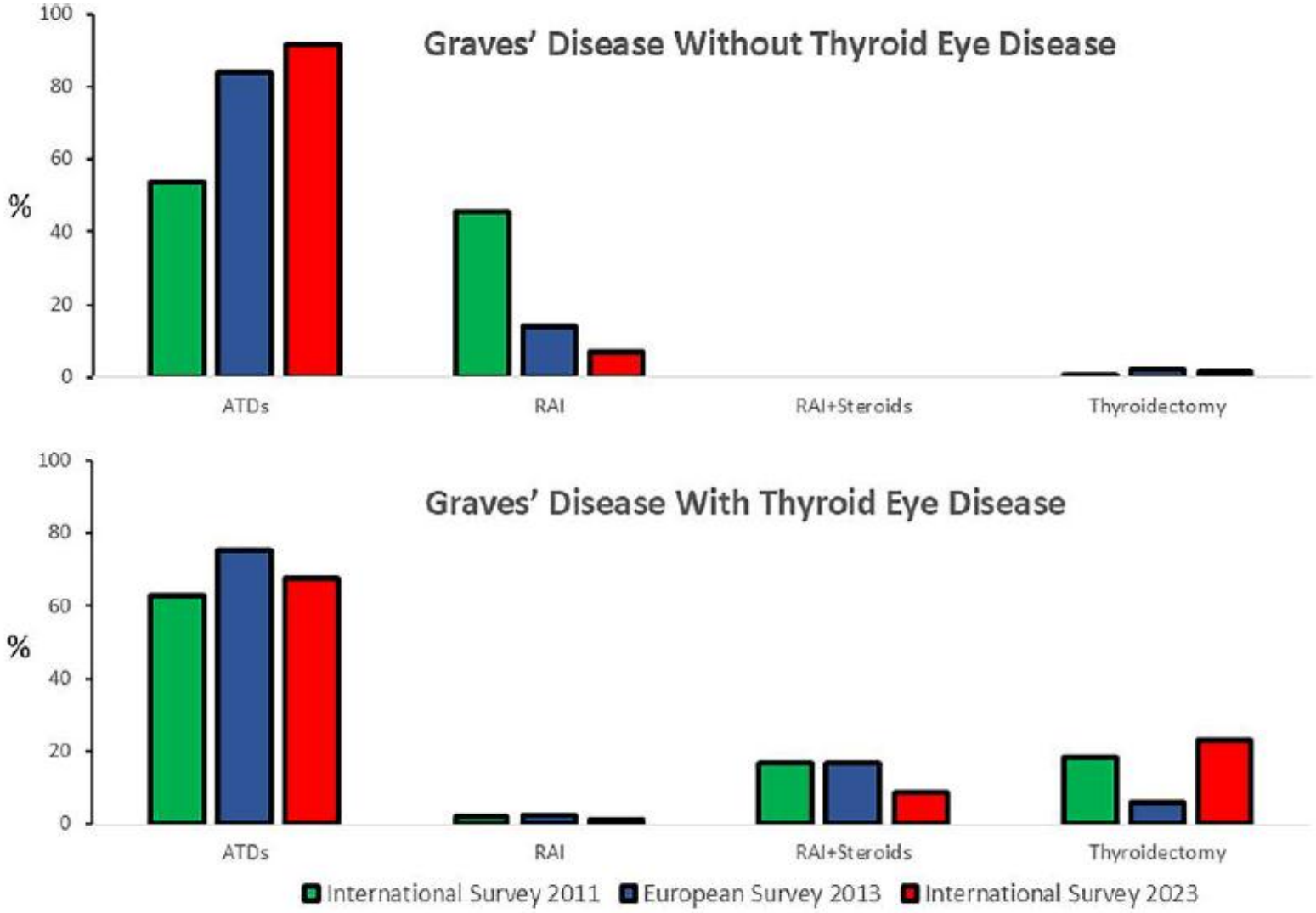


Figure 1. Preferred treatment for hyperthyroidism without or with moderate to severe and active thyroid eye disease in 3 independent surveys conducted from 2011 to 2023. Derived from Burch et al (36), Bartalena et al (37), Villagelin et al (38).

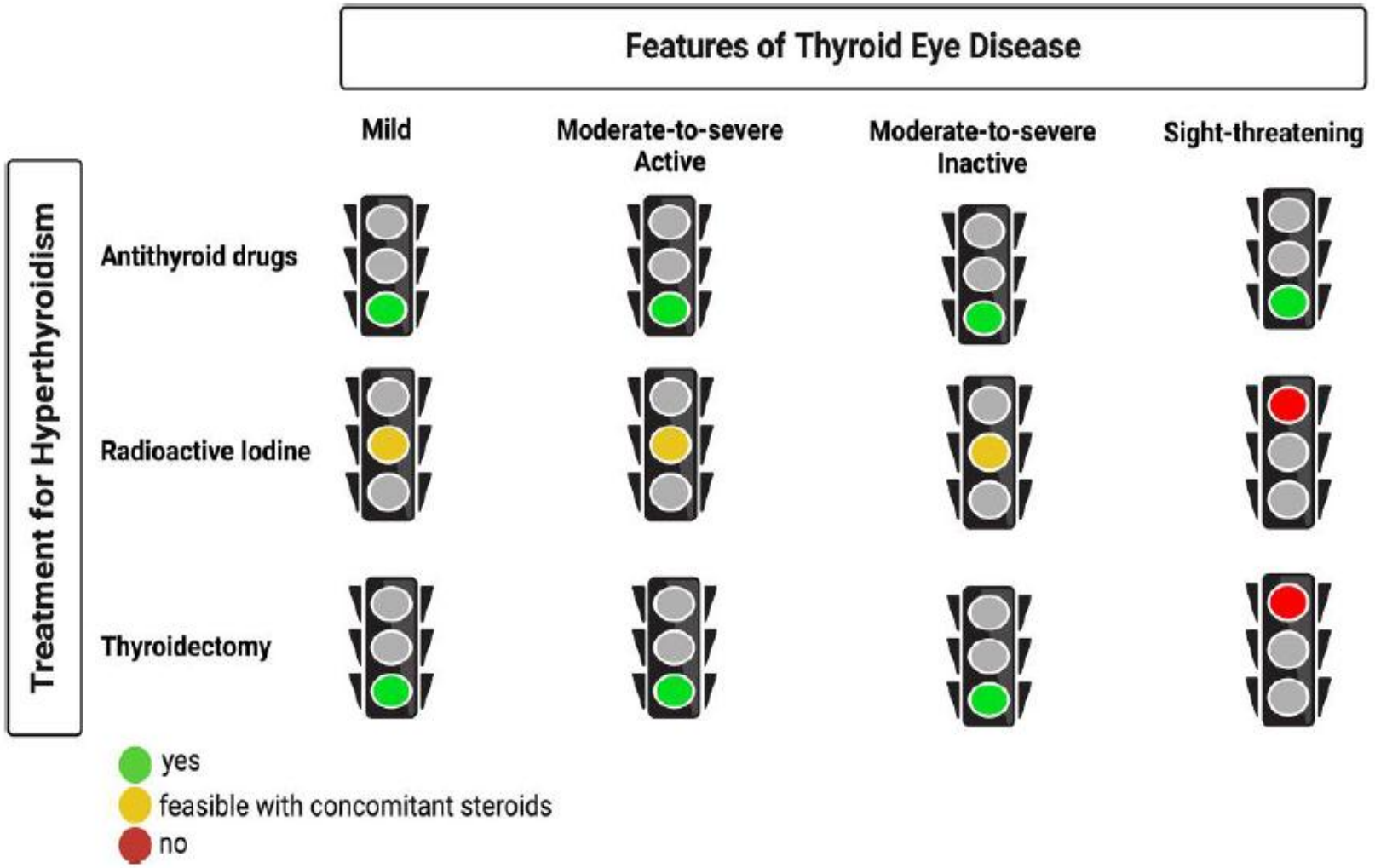


Figure 2. Relation between features of TED and therapies for hyperthyroidism associated with Graves' disease. Green light: treatment is indicated. Yellow light: treatment should be used with caution, in association with low-dose oral steroid prophylaxis in the case of mild TED or concomitant high-dose intravenous glucocorticoid treatment in the case of moderate to severe and active TED. Red light: avoid this treatment. Indications concerning the use of radioactive iodine in patients with moderate to severe and active TED deviate from recommendatons of current consensus-driven guidelines but find support by reanalysis of 3 randomized clinical trials (see text).

Table 1. Effects of treatments for Graves' hyperthyroidism on TED

Treatment for hyperthyroidism	TED	Reference
Antithyroid drugs	• No direct effect • Restoration of euthyroidism is associated with amelioration of mild TED	• Bartalena et al (22) • Prummel et al (19)
RAI	• Progression of mild TED in 15% of cases after RAI, preventable by steroid prophylaxis	• Bartalena et al (22)
	• No deterioration after RAI in moderate to severe and active TED concomitantly treated with high-dose glucocorticoids	• Marcocci et al (51); Menconi et al (52); Moleti et al (53)
Surgical thyroidectomy	• Neutral effect • Uncertain beneficial effect of early surgery	• Marcocci et al (54) • Erdogan et al (55); Mayer Zu Horste et al (56)

Abbreviations: RAI, radioactive iodine; TED, thyroid eye disease.

Effects of Treatment for Hyperthyroidism on TED

ATD

- natural course of TED appears unaffected by ATD treatment, and those beneficial effects frequently reported are likely indirect, due in large part to restoration of euthyroidism

- control of hyperthyroidism and careful maintenance of euthyroidism in patients with TED is recommended by clinical practice guidelines

RAI

- treatment can cause worsening of mild TED or its de novo development.
- RAI treatment is frequently followed by a marked increase in circulating TSHR-Ab, sometimes lasting for several years
- Risk factors for RAI-associated TED progression include:
  - recent-onset hyperthyroidism
  - severe and uncontrolled hyperthyroidism
  - high TSHR-Ab levels,
  - tobacco smoke
  - delayed correction of post-RAI hypothyroidism
  - preexisting TED

Effects of Treatment for Hyperthyroidism on TED

- In a randomized clinical trial, prednisone administered at 0.4 ro 0.5 mg/ starting 2 to 3 days after RAI administration, followed by a 3-month taper, was shown to be protective against TED
- In a retrospective matched-cohort study, lower doses of prednisone (0.16-0.27 mg/kg) and a shorter duration (6 weeks) were shown to be equally effective against TED worsening following RAI, if the patient was not at high risk of progression (smoker, severe and unstable hyperthyroidism, high TSHR-Ab levels)

- "steroid prophylaxis" is recommended in patients undergoing RAI treatment in the presence of preexisting mild TED and/or risk factors

Effects of Treatment for Hyperthyroidism on TED

Thyroidectomy

- surgical thyroidectomy appears to be devoid of associated deleterious changes in the course of TED and might improve outcomes
- Total thyroid ablation (ie, thyroidectomy followed by RAI remnant ablation) may be associated with a more favorable short-term effect of IV glucocorticoid therapy for moderate to severe TED compared to total thyroidectomy alone
- Any such ameliorative effect does not appear to persist long term .

MILD GO

General recommendations

- Refrain from smoking
- Treat thyroid dysfunction (preferably with antithyroid drugs, especially if risk factors for deterioration/progression of GO are present (see below)
- Avoid iatrogenic hypothyroidism in treating patients with GD/GO
- Referral to thyroid-eye clinics if risk factors present (active GO, smoker, high TSHR-Ab, unstable / severe hyperthyroidism)
- Search for dry eye syndrome

Management

Local treatment

- Artificial tears, especially when dry eye present
- Ophthalmic gels (cornea protection during the night)

Systemic adjunct therapy for active GO

- Selenium supplementation for six months (fasting intake)

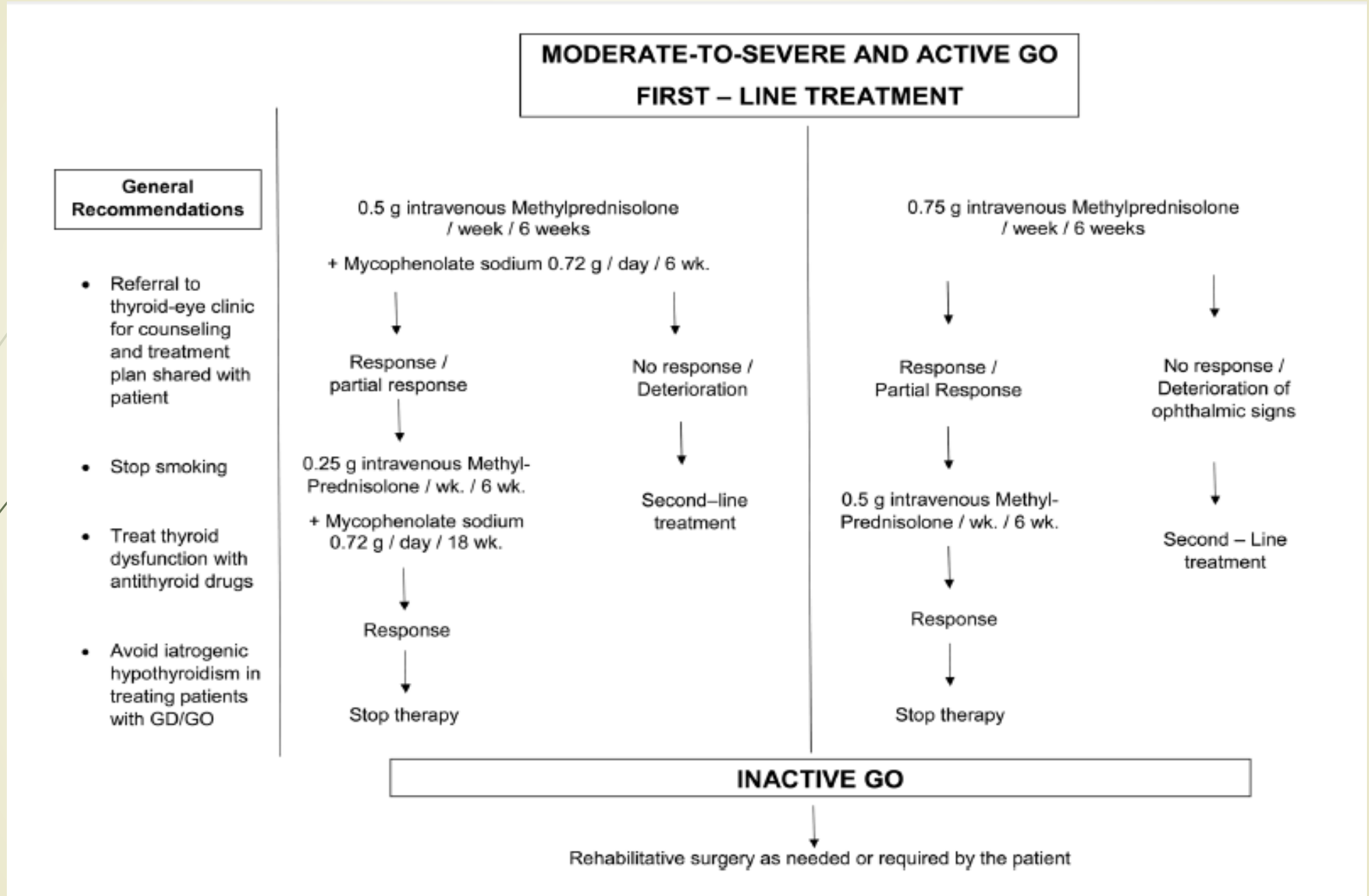
Quality of life markedly impaired

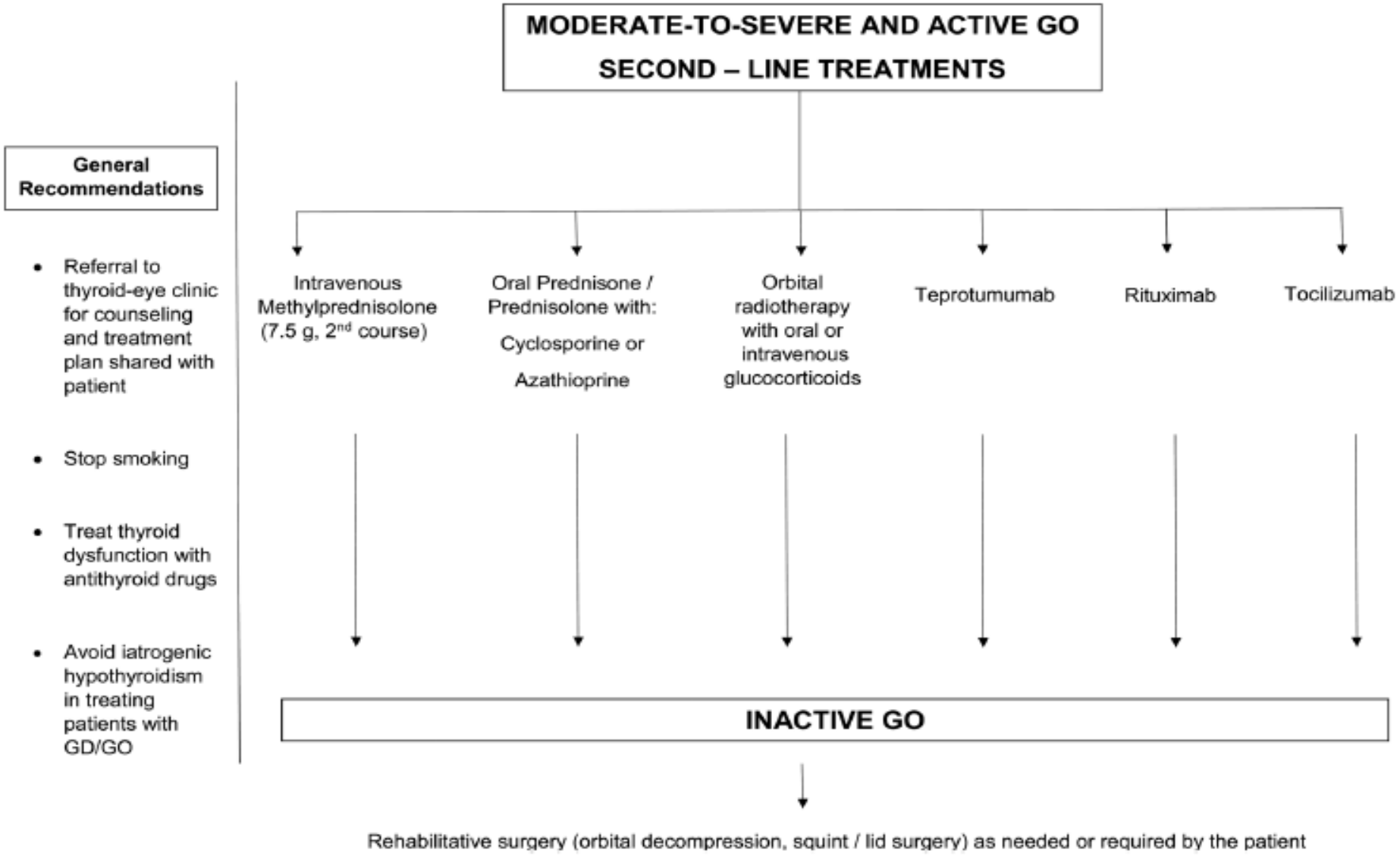
↓

Discuss low dose immunomodulatory (active GO) or rehabilitative surgery (inactive GO) following extensive counseling and shared decision

Mild TED

- Mild forms represent the large majority of patients with TED, accounting for 76% of patients with newly diagnosed GD who develop eye disease
- managed by a "wait-and-see" strategy, local treatment (artificial tears, ointments), and control of modifiable risk factors
- A 6-month selenium supplementation
- A preference for ATD (possibly long-term) treatment or thyroidectomy.
- RAI in patients with GD complicated by mild TED, steroid prophylaxis should be initiated, as this treatment prevents TED progression
- RAI treatment should not be considered contraindicated in patients with mild TED, especially in those whose disease developed in the distant past


MODERATE-TO-SEVERE AND ACTIVE GO
FIRST – LINE TREATMENT
General Recommendations
Referral to thyroid-eye clinic for counseling and treatment plan shared with patient
Stop smoking
Treat thyroid dysfunction with antithyroid drugs
Avoid iatrogenic hypothyroidism in treating patients with GD/GO
0.5 g intravenous Methylprednisolone / week / 6 weeks
+ Mycophenolate sodium 0.72 g / day / 6 wk.
Response / partial response
0.25 g intravenous Methyl-Prednisolone / wk. / 6 wk.
+ Mycophenolate sodium 0.72 g / day / 18 wk.
Response
Stop therapy
No response / Deterioration
Second–line treatment
0.75 g intravenous Methylprednisolone / week / 6 weeks
Response / Partial Response
0.5 g intravenous Methyl-Prednisolone / wk. / 6 wk.
Response
Stop therapy
No response / Deterioration of ophthalmic signs
Second – Line treatment
INACTIVE GO
Rehabilitative surgery as needed or required by the patient


MODERATE-TO-SEVERE AND ACTIVE GO
SECOND – LINE TREATMENTS
General Recommendations
Referral to thyroid-eye clinic for counseling and treatment plan shared with patient
Stop smoking
Treat thyroid dysfunction with antithyroid drugs
Avoid iatrogenic hypothyroidism in treating patients with GD/GO
Intravenous Methylprednisolone (7.5 g, 2nd course)
Oral Prednisone / Prednisolone with:
Cyclosporine or
Azathioprine
Orbital radiotherapy with oral or intravenous glucocorticoids
Teprotumumab
Rituximab
Tocilizumab
INACTIVE GO
Rehabilitative surgery (orbital decompression, squint / lid surgery) as needed or required by the patient

Moderate to severe and active TED

- 10% of all cases
- high- dose glucocorticoids alone or in combination with orbital radiotherapy or other immunosuppressive agents
- Teprotumumab
  - highly effective, especially for improving proptosis and diplopia.
  - 8 infusions over 24 weeks
  - improve proptosis, diplopia, clinical activity score, and quality of life
  - preferred treatment when proptosis and diplopia are prominent features of TED
  - monoclonal inhibitory Ab of IGF-I receptor tyrosine kinase activity
  - only drug approved by the FDA for the treatment of TED.
- rituximab and tocilizumab have failed to establish sound efficacy of either as a first-line treatment, although they are a valid option as a second-line treatment.
- batoclimab (an antineonatal Fc receptor monoclonal antibody) are currently under investigation

ATA 2024 Meeting

Batoclimab

- a monoclonal Ab targeting FcRn , is designed to reduce IgG levels, while decreasing the TRAb levels that are key culprits in GD, as well as TED
- For the phase 2a, 27 patients who remained hyperthyroid despite having been treated with methimazole at doses of 10 mg or more per day for at least 12 weeks
- All the patients had T4 and/or T3, as well as TRAb levels that were above the upper limit of normal at baseline.
- All received batoclimab sc of 680 mg/wk for 12 weeks, followed by 340 mg/wk for another 12 weeks. Of the patients,
- Most patients (80%) had preexisting Graves' orbitopathy
- By week 12, more than half of patients had both T3 and T4 below the ULN and were off ATD. Batoclimab also improved extrathyroidal signs."
- Thyroid volume was decreased by 9 mL from baseline at 24 weeks, and proptosis was reduced by 2.5 mm at 12 weeks and 3 mm at 24 weeks.

Moderate to severe and active TED

- ATDs are the preferred treatment, since they do not negatively impact the orbital disease course
- Thyroidectomy can be considered, but timing can be difficult when intravenous glucocorticoids or teprotumumab are employed
- the safety of teprotumumab administered proximate to surgery and the potential for affecting wound healing has not been studied.
- guidelines suggest avoiding RAI treatment in patients with moderate to severe and active TED ,this modality may be considered, provided concomitant treatment of TED with high-dose glucocorticoids as monotherapy or combined with orbital radiotherapy is given (Fig. 2).
- Whether teprotumumab has a similar effect in patients treated with RAI remains unexplored.

Moderate to Severe and Inactive TED

- Patients with longstanding moderate to severe and inactive TED have been traditionally considered as unresponsive to medical treatment
- teprotumumab appears to be effective
- These cases are unlikely to experience disease flares even after RAI treatment
- Accordingly, any treatment for hyperthyroidism can be used
- According to European Group on GO guidelines ,if risk factors for a flare of TED exist (cigarette smoking, high serum TSHR-Ab), steroid prophylaxis should be considered if the patient undergoes treatment with RAI.

SIGHT - THREATENING GO (Optic Neuropathy)

General recommendations

- Immediate referral to thyroid-eye clinic
- Stop smoking
- Avoid radioactive iodine treatment
- Stabilize thyroid dysfunction with antithyroid drugs
- Avoid iatrogenic hypothyroidism in treating patients with GD/GO

Specific Management

Intravenous methylprednisolone (0.5 – 1 gram, as single dose repeated on three consecutive or alternate days)

↓

Daily monitoring of ophthalmic parameters

↓

After one week, evaluation if therapy can be continued

↓ Yes

↓

Further with intravenous methylprednisolone as in week one

↓ Response

↓

0.5 g intravenous methylprednisolone 1x / wk. (cumulative dose <8 g / cycle)

↓ Partial response

↓

Urgent orbital decompression surgery (Imaging recommended)

↓ No response and/or deterioration of ophthalmic signs

↓

Urgent orbital decompression surgery (Imaging recommended)

Sight-threatening TED

- Very severe TED : dysthyroid optic neuropathy or corneal breakdown
- risk of vision loss.

- an emergency and treated very high doses of IV glucocorticoids and/or urgent orbital decompression

- Treatment of TED is an absolute priority, and management of associated hyperthyroidism is delegated to ATDs (Fig. 2)

- progression of TED to proceed independently of the processes underlying thyroid gland dysfunction in GD.
- any available treatment for hyperthyroidism can prevent the occurrence of TED.
- treatment of TED does not appear to impact the course of hyperthyroidism .Rituximab a possible exception. This agent reduced TED activity but not severity .

Subclinical hyperthyroidism

- TSH <0·1 mU/L
  - In patients with a TSH <0·1 mU/L, thyroid dysfunction usually persists or progresses to overt hyperthyroidism.
  - older patients with SCH have increased risks of cardiovascular disease (AF, HF, CHD, stroke) ,hip and other fractures, osteoporosis, and mortality, and dementia.
  - in older patients, SCH is more prevalent than overt hyperthyroidism.
  - guidelines recommend treatment of SCH with a serum TSH <0 ▪ 1 mU/L, independent of the presence of symptoms, particularly in elderly patients.

- TSH between 0·1 -0·4 mU/L (mild SCH),:
  - TSH concentrations normalize during follow-up in 20–30% of individuals over 4·5–5 years.
  - there is no consensus regarding treatment for patients with mild SCH

- treat severe and possibly mild SCH in people >65 years, despite little high-quality evidence of therapeutic benefits.
- When treatment is started, the goal is to normalize serum TSH concentrations

Thyroiditis

- Thyrotoxicosis caused by thyroiditis :
  - transient and self-limiting, regardless of cause
  - no treatment is required.
  - β blockers provide symptomatic relief, but ATD are ineffective and not indicated.
- For SAT
  - first-line treatment is NSAID
  - glucocorticoid treatment used if symptoms are severe or the patient does not respond to NSAID.
  - Prednisolone or prednisone 30–40 mg daily for 1–2 weeks followed by dose tapering is widely used,
  - lower initial doses (15–20 mg) can be effective.
  -
- Thyrotoxicosis is often followed by hypothyroidism (transient or permanent).
  - lymphocytic thyroiditis (including post partum), hypothyroidism can be long lasting (6–12 m) or permanent in 10–40% of cases
  - SAT : most patients recover normal thyroid function
  - Levothyroxine replacement is indicated if hypothyroidism is severe or symptomatic, with consideration of a trial of withdrawal of therapy after 6–12 months.
  - Thyroiditis caused by checkpoint inhibitor is followed by permanent hypothyroidism in most cases