HYPERTHYROIDISM

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Original Hyperthyroidism Clinical Guidance- Issued April 2020

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Abbreviations

Anti-TSH-R	Anti-Thyroid Stimulating Hormone Receptor
ATD	Antithyroid Drug
Beta-AA	Beta-Adrenergic Receptor Antagonist
BR	Block and Replace
CADTH	Canadian Agency for Drugs and Technologies in Health
CBZ	Carbimazole
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
DT	Dose Titration
FDA	Food and Drug Administration
FT3	Free Triiodothyronine
FT4	Free Thyroxine
GD	Grave's Disease
GO	Graves' Orbitopathy
HAS	Haute Authorite de Sante
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care
LT4	Levothyroxine
MMI	Methimazole
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PPT	Postpartum Thyroiditis
PTU	Propylthiouracil
RAI	Radioiodine
SFDA	Saudi Food and Drug Authority
TBII	TSH-binding inhibitor immunoglobulin
TPE	Therapeutic plasmapheresis
TPO-Ab	Anti-Thyroid Peroxidase Antibodies
TRAb	Thyroid receptor antibodies
TSH	Thyroid-stimulating hormone
TSHRAb	Thyrotropin (TSH) receptor antibodies
TT3	Total triiodothyronine

Executive Summary

Hyperthyroidism encompasses a group of medical conditions characterized by an excessive production and release of thyroid hormones by the thyroid gland. This excess leads to elevated levels of free thyroxine (FT4), free triiodothyronine (FT3), or both in the bloodstream, resulting in a state of hypermetabolism known as thyrotoxicosis. The most prevalent types of hyperthyroidism comprise diffuse toxic goiter, commonly known as Graves' disease, toxic multinodular goiter, often referred to as Plummer's disease, and toxic adenoma[1].

Graves' disease is the most prevalent type of hyperthyroidism in the United States, responsible for around 60-80% of cases of thyrotoxicosis. Over a 20-year period, the annual incidence of Graves' disease was determined to be 0.5 cases per 1000 population, with the highest occurrence observed among individuals aged 20-40 years[1]. The prevalence of suspected cases of hyperthyroidism was evaluated in a cross-sectional study Jeddah by Using Wayne's Scoring Index. During a health awareness campaign lasting five days, a total of 346 participants were conveniently chosen from two shopping centers in Jeddah city. The study included 194 women (56.1%) and 152 men (43.9%). The participants' ages ranged from 16 to 56 years. Wayne's scores showed 80.6% were euthyroid, 18.2% equivocal, and 1.2% have hyperthyroidism[2].

The main symptoms of hyperthyroidism and thyrotoxicosis include anxiety, nervousness, increased perspiration, heat intolerance, hyperactivity, and palpitations. The most reliable screening measure of thyroid function is the thyroid-stimulating hormone (TSH) level. TSH levels usually are suppressed to unmeasurable levels (< 0.05 μIU/mL) in thyrotoxicosis. The degree of thyrotoxicosis is determined by measurement of thyroid hormone levels; the severity of clinical manifestations often does not correlate with the degree of thyroid hormone elevation[1].

The management of hyperthyroidism and thyrotoxicosis involves alleviating symptoms. In addition to symptom relief, hyperthyroidism necessitates antithyroid medication, radioactive iodine-131 (131I) therapy (which is the favored approach for treating hyperthyroidism according to US thyroid experts), or thyroidectomy[1].

Graves' orbitopathy (GO) is an orbital autoimmune disorder and the main extrathyroidal manifestation of Graves' disease, the most common cause of hyperthyroidism. GO affects about 30% of Graves' patients, although fewer than 10% have severe forms requiring immunosuppressive treatments. Management of GO requires a multidisciplinary approach. Medical therapies for active moderate-to-severe forms of GO (traditionally, high-dose glucocorticoids) often provide unsatisfactory results, and subsequently surgeries are often needed to cure residual manifestations.[3] This disorder will also be discussed briefly in the report.

CHI issued a hyperthyroidism clinical guidance after thorough review of renowned international and national clinical guidelines in May 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Hyperthyroidism Clinical Guidance and seeks to offer guidance for the effective management of hyperthyroidism. It provides an update on the hyperthyroidism guidelines for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized being **the issuance of updated versions of previously reviewed guidelines** namely **NICE** Guideline on Assessment and Management of Thyroid Disease (Published 2019, Updated **2023**). Moreover, new **guidelines are added to the report** such as **2022 European Thyroid Association Guideline** for the management of pediatric Graves' disease, the **French Consensus** on the Treatment of adult Graves' disease **(2018)**, the **French Consensus** on Graves' disease and pregnancy **(2018)**, the **2017 Guidelines of the American Thyroid Association** for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum, the **2021 European Group on Graves' orbitopathy (EUGOGO)** clinical practice guidelines for the medical management of Graves' orbitopathy and **2016** Guidelines for the management of thyroid storm from **The Japan Thyroid Association and Japan Endocrine Society (First edition)**.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is recommended to add metoprolol tartrate in the form of film-coated tablets, azathioprine, rituximab, tocilizumab, prednisone, and prednisolone to the SFDA list.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Hyperthyroidism management.

Below is a table summarizing the major changes based on the hyperthyroidism guidelines used to issue this report:

Table 1. General Recommendations for the Management of Hyperthyroidism

Management of Hyperthyroidism		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: RAI therapy, ATDs, or thyroidectomy.	Strong recommendation, moderate-quality evidence	American Thyroid Association Guidelines (2016)[4]
When managing hyperthyroidism, thiamazole and carbimazole are the preferred options, with the exception being the first trimester of pregnancy or when planning for pregnancy.	1/++	French Consensus on the Treatment of adult Graves' disease (2018)[5]
For patients who remain thyrotoxic despite receiving large doses of CBZ (≥1.3 mg/kg/day) or MMI (≥1 mg/kg/day), alternative treatment options such as surgery or radioactive iodine (RAI) should be discussed.	1,ØØØO	European Thyroid Association Guideline (2022)[6]
Surgery is recommended when medical treatment fails or when complications arise.	2/+	French Consensus on the Treatment of adult Graves' disease (2018)[5]
The preferred primary approach is total thyroidectomy.	1/+	French Consensus on the Treatment of adult Graves' disease (2018)[5]
Patients with noticeable symptoms of elevated thyroid hormone levels are advised to utilize beta-adrenergic blockers. These blockers can be discontinued when the patient reaches a state of biochemical euthyroidism.	1,ØØØO	European Thyroid Association Guideline (2022)[6]
Prior to starting radioiodine therapy, it is advisable to systematically commence beta-blocker treatment in individuals who are manifesting	1/++	French Consensus on the Treatment of adult Graves' disease (2018)[5]

symptomatic hyperthyroidism. This precaution is taken due to the possible risk of a temporary exacerbation of hyperthyroidism following radioiodine treatment, especially in cases where antithyroid drugs are contraindicated or not well-tolerated.		
Radioiodine therapy is contraindicated during pregnancy.	1/++	French Consensus on Graves' disease and pregnancy (2018)[7]
Fetal hyperthyroidism is managed through maternal antithyroid therapy.	1/+	French Consensus on Graves' disease and pregnancy (2018)[7]

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI hypertension report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the April 2020 CHI Hyperthyroidism Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old Versions	**Updated Versions**
NICE Guideline on Assessment and Management of Thyroid Disease (**2019**)	**NICE** Guideline on Assessment and Management of Thyroid Disease (Published 2019, Updated **2023**)
European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism (**2018**)	Not available
American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis (**2016**)	Not available

1.1.1 NICE Guideline on Assessment and Management of Thyroid Disease (Published 2019, Updated 2023)

The National Institute for Health and Care Excellence (NICE) originally published a guidance on the assessment and management of thyroid disease in 2017. This guidance was updated in October 2023 and the main recommendations are detailed below[8]:

Managing thyrotoxicosis

A- Tests for people with confirmed thyrotoxicosis

✓ **Adults:**

- Distinguish between cases of thyrotoxicosis with hyperthyroidism (such as Graves' disease or toxic nodular disease) and cases of thyrotoxicosis without hyperthyroidism (such as transient thyroiditis) in adults by following these steps:
    i. Confirm Graves' disease by conducting tests for TSH receptor antibodies (TRAbs).
    ii. If TRAbs yield negative results, contemplate the use of technetium scanning for thyroid gland assessment.
- Only contemplate the use of ultrasound in adults with thyrotoxicosis if they present with a palpable thyroid nodule.

✓ **Children and young people:**

- In children and young individuals, differentiate between cases of thyrotoxicosis with hyperthyroidism (specifically, Graves' disease) and those without hyperthyroidism (e.g., transient thyroiditis) by employing the following strategies:
    i. Assess the levels of thyroid peroxidase antibodies (TPOAbs) and TSH receptor antibodies (TRAbs).
    ii. If TRAbs produce negative results, consider utilizing technetium scanning to examine the thyroid gland.
- Moreover, reserve the use of ultrasound for children and young individuals with thyrotoxicosis if they either present a palpable thyroid nodule or if the cause of thyrotoxicosis remains unclear after conducting tests for thyroid autoantibodies and technetium scanning.

Initial treatment in primary/non-specialist care

- Recognize that transient thyrotoxicosis without hyperthyroidism typically requires only supportive care, such as the use of beta-blockers.
- For adults with hyperthyroidism who are awaiting specialist evaluation and additional treatment, contemplate the use of antithyroid medications in conjunction with supportive care.
- Note: Use of carbimazole is subject to MHRA advice on contraception and risk of acute pancreatitis.

Initial treatment in secondary/specialist care

- Engage in a conversation with adults, children, and young individuals who have thyrotoxicosis with hyperthyroidism (along with their families and caregivers when relevant) regarding:
    i. The potential advantages and disadvantages associated with various treatment choices, including antithyroid drugs, radioactive iodine, and surgery.
    ii. The probability of a favorable response to each treatment option.
- Consider providing antithyroid medications to manage hyperthyroidism in adults, children, and young individuals who are in the process of waiting for radioactive iodine or surgical treatment.
- Note: Carbimazole use is off label for children under 2 years.

Adults with Graves' disease

- Provide radioactive iodine as the primary, definitive treatment option for adults with Graves' disease, except in the following situations:
    i. When antithyroid drugs are likely to lead to remission
    ii. When it is not suitable due to reasons such as concerns about compression, suspicion of thyroid malignancy, pregnancy or plans to conceive in the next 4 to 6 months, or the presence of active thyroid eye disease.
- For adults with Graves' disease, a choice between a 12- to 18-month course of antithyroid drugs or radioactive iodine can be offered as the initial definitive treatment if antithyroid drugs are expected to achieve remission, especially in cases of mild and uncomplicated Graves' disease.
- Antithyroid drugs, given over a 12- to 18-month course, can be offered as the primary definitive treatment for adults with Graves' disease if radioactive iodine and surgery are not suitable options.
- In cases where there are concerns about compression or suspicion of thyroid malignancy, or when both radioactive iodine and antithyroid drugs are not suitable, consider total thyroidectomy as the first-line definitive treatment for adults with Graves' disease.
- Additionally, for adults with Graves' disease who have received antithyroid drugs but still experience persistent or recurring hyperthyroidism, contemplate the use of radioactive iodine or surgery as treatment options.

Adults with toxic nodular goitre

- Provide radioactive iodine as the primary, definitive treatment for adults with hyperthyroidism resulting from multiple nodules, unless specific conditions make it unsuitable. Unsuitability may arise, for instance, due to concerns about compression, suspected thyroid malignancy, pregnancy or plans to conceive in the next 4 to 6 months, or the presence of active thyroid eye disease.
- For adults with hyperthyroidism due to multiple nodules where radioactive iodine is not a suitable option, offer either total thyroidectomy or a lifelong course of antithyroid drugs as the initial definitive treatment.
- In cases of hyperthyroidism resulting from a single nodule in adults, consider radioactive iodine (if appropriate) or surgical treatment (hemithyroidectomy) as the primary definitive approaches. If these options are not suitable, a lifelong course of antithyroid drugs can be considered.

Children and young people with Graves' disease or toxic nodular goitre

- Provide antithyroid drugs as the primary, definitive treatment for children and young individuals with Graves' disease, and maintain this treatment for at least 2 years, with the possibility of extending it beyond that period.
- In cases where children and young people with Graves' disease experience a relapse of hyperthyroidism after a course of antithyroid drugs, consider one of the following options:
    i. Continue or restart antithyroid drugs
    ii. Engage in discussions about the use of radioactive iodine or the consideration of surgery, specifically total thyroidectomy.
- For children and young individuals with hyperthyroidism stemming from a single or multiple nodules, the following approach should be considered:
    i. Offer antithyroid drugs using a titration regimen of carbimazole.
    ii. Engage in discussions about the potential roles of surgery and radioactive iodine, involving the child, young person, and their family, following input from a multidisciplinary team.

Antithyroid drugs for adults, children, and young people with hyperthyroidism

- Before initiating antithyroid drugs for individuals of various age groups with hyperthyroidism, conduct a complete blood count and liver function tests.
- When considering antithyroid drugs as the primary, definitive treatment for adults with Graves' disease, provide carbimazole for a duration of 12 to 18

months, utilizing either a block and replace or titration regimen, and subsequently evaluate the necessity for continued treatment. In the case of children and young people with Graves' disease, offer carbimazole with a titration regimen and reassess the need for treatment every 2 years.

- For adults with hyperthyroidism due to single or multiple toxic nodules, contemplate lifelong antithyroid drug treatment using a titration regimen of carbimazole.
- Consider the use of propylthiouracil for adults under the following circumstances:
    i. Those who exhibit adverse reactions to carbimazole.
    ii. Those who are pregnant or planning to conceive within the next 6 months.
    iii. Those with a history of pancreatitis.
- If an individual develops agranulocytosis while on antithyroid drugs, discontinue the medication and do not restart it. It is advisable to consider referring the individual to a specialist for further management options.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Hyperthyroididsm report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
2022 European Thyroid Association Guideline for the Management of Pediatric Graves' Disease
French Consensus on the Treatment of Adult Graves' disease **(2018)**
French Consensus on Graves' Disease and Pregnancy **(2018)**
2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum
The 2021 European Group on Graves' orbitopathy (EUGOGO) Clinical Practice Guidelines for the Medical Management of Graves' Orbitopathy
2016 Guidelines for the management of thyroid storm from **The Japan Thyroid Association and Japan Endocrine Society (First edition)**

1.2.1 European Thyroid Association Guideline for the Management of Pediatric Graves' Disease (2022)

The European Thyroid Association (ETA) guideline published in 2022 addresses the etiology, diagnosis, and prognosis of pediatric Graves' disease patients with and without orbitopathy and includes evidence-based treatment recommendations[6].

Table 4. Quality of Evidence Recommendations as Defined by GRADE

Quality of Evidence	
Level 'ØØØØ'	High
Level 'ØØØO'	Moderate
Level 'ØØOO'	Low
Level 'ØOOO'	Very low

Table 5. Grading Scheme for Recommendations

Grading Scheme for Recommendations	
1	Strong recommendation
2	Weak recommendation or suggestion

- In the case of suspected hyperthyroidism in pediatric patients, it is advisable to conduct tests for serum levels of free thyroxine (FT4), free- triiodothyronine (FT3), and thyroid-stimulating hormone (TSH). Given that Graves' disease (GD) is the most common underlying cause of hyperthyroidism, it is recommended to also perform assessments for anti-TSH receptor antibodies (TSHRAb, also referred to as thyroid-binding inhibitory immunoglobulin or TBII) and anti-thyroperoxidase antibodies (anti-TPO).

Medical treatment of hyperthyroidism caused by Graves' disease (GD)

- In pediatric patients suspected of having hyperthyroidism, it is advisable to promptly initiate treatment (1,ØØØØ).
- For young individuals with hyperthyroidism due to Graves' disease (GD), either carbimazole (CBZ) or its active form, methimazole (MMI), should be used. Propylthiouracil should be avoided (1,ØØØØ).
- The initial dosage of antithyroid drugs (ATDs) should range from 0.15 to 0.5 mg/kg for MMI or 0.25 to 0.75 mg/kg for CBZ, given once daily (1,ØØØO).
- When employing a dose titration (DT) approach, most patients achieve normalized thyroid hormone levels within the initial 4–6 weeks with a starting

dose of 0.15–0.3 mg/kg for MMI or 0.25–0.5 mg/kg for CBZ. Dose reductions of 25–50% based on thyroid function tests are recommended, and higher ATD doses may be considered for severe cases (1,ØØØO).

- Treatment adjustments may not be necessary if FT4 or FT3 levels are relatively high and TSH remains within the normal range (1,ØOOO).
- Educating patients about GD and its treatment is essential to enhance compliance, taking into account their developmental stage (1,ØØOO).
- In the block and replace (BR) strategy, a dose of 0.3–0.5 mg/kg for MMI or 0.5–0.75 mg/kg for CBZ effectively inhibits endogenous thyroid hormone production. Levothyroxine can be introduced at an age and weight-appropriate replacement dose once FT3 levels fall within the reference range. Higher ATD doses may be required if thyroid hormone concentrations, particularly FT3, do not decrease as expected (1,ØØØO).
- In most cases, a dose titration (DT) approach is the preferred method for ATD treatment (1,ØØØO).
- It is advisable to use beta-adrenergic blockade in patients presenting with pronounced signs of excess thyroid hormone. This can be discontinued once the patient attains biochemical euthyroidism (1,ØØØO).
- Patients with untreated GD may experience severe illness characterized by prominent signs of thyroid hormone excess, necessitating management in a high dependency or intensive care unit (1,ØØØO).
- Patients managed with DT or BR should undergo evaluations approximately every 4 weeks during the initial 3 months, transitioning to 2 and subsequently 3-month assessments depending on the clinical course (1,ØØØO).
- Baseline assessments, including white blood cell count, neutrophil count, and liver function tests, should be conducted because both can be influenced by the underlying disease process and ATD therapy (1,ØØØO).
- Thyroid hormone concentrations (FT4 and FT3) should typically normalize within the first 6 weeks, with noticeable improvement in the initial 4 weeks. TSH suppression may persist for several months (1,ØØØO).
- Families should be cautioned about the potential for excessive weight gain during ATD therapy (1,ØØØO).
- Minor side effects of ATDs occur in 10 to 20% of patients and are generally transient. Serious side effects warranting ATD discontinuation are rare (1,ØØØO).

- Patients and families should receive counseling regarding ATD side effects and the criteria for discontinuing the drug and seeking guidance from healthcare professionals (1,ØØØØ).
- For patients who remain thyrotoxic despite receiving large doses of CBZ (≥1.3 mg/kg/day) or MMI (≥1 mg/kg/day), alternative treatment options such as surgery or radioactive iodine (RAI) should be discussed (1,ØØØO).
- Definitive treatment (total thyroidectomy or RAI) should be considered for patients who develop severe neutropenia, significant liver dysfunction, troublesome side effects that do not resolve, or when prolonged ATD therapy has not resulted in remission. It may also be appropriate when patients cannot accurately report potential ATD side effects or face compliance issues (1,ØØØØ).
- TSH receptor antibodies (TSHRAb) can be utilized to predict the likelihood of remission. Elevated TSHRAb levels indicate a low probability of remission, and discontinuing ATD therapy is not recommended (1,ØØØO).
- Typically, ATD treatment is administered for at least 3 years and should be discontinued only when TSHRAb levels have consistently been low for several months. Longer courses of ATD treatment (≥5 years) may be considered in cases where the likelihood of remission is low based on initial disease characteristics (1,ØØØO).
- The overall remission rate in pediatric GD patients after 2 years of ATD treatment is approximately 20-30% and may increase with continued ATD therapy (1,ØØØØ).
- When discontinuing ATD treatment, it is important to discuss the signs of thyroid hormone excess and establish a pathway for thyroid function testing (1,ØØØO).
- Patients who experience a relapse after completing a course of ATD treatment can choose to either resume ATD therapy or opt for definitive treatment. This decision may be influenced by factors such as age or educational stage (1,ØØØO).
- There is currently no established role for immune modulation using new agents like biologics in young individuals with GD (1,ØØØO).

Definitive treatment in pediatric GD – radioiodine (RAI)

- The primary aim of radioactive iodine (RAI) treatment (I-131) is to achieve complete thyroid ablation, a critical step to prevent both relapse and the potential development of thyroid cancer (1,ØØOO).

- It is advisable to avoid administering RAI to patients younger than 5 years old. However, for the age group between 5 and 10 years, RAI may be considered when surgery is not a feasible option. There are no contraindications to using RAI in patients older than 10 years or post-pubertal children (1,ØØOO).
- Ideally, RAI activity should be customized based on individual needs. When dosimetry calculations are challenging, a recommended activity is 15 MBq (0.4 miCi) per gram of thyroid tissue. Alternatively, when dosimetry is available, the aim should be to deliver at least 300 Gy to the thyroid gland. To calculate the I-131 dose accurately, thyroid weight is best estimated using ultrasound (2,ØØØO).
- Prior to undergoing RAI treatment, it is important to discontinue antithyroid drugs (ATD) for a period of 3–7 days (1,ØØØO).
- The administration of RAI therapy should be avoided if a patient presents with active Graves' orbitopathy (GO). In cases of inactive GO, it is recommended to concurrently provide a course of steroids to prevent relapse or exacerbation (1,ØØØØ).

Definitive treatment in pediatric Graves' disease – thyroidectomy

- Pediatric patients scheduled for thyroidectomy should be operated on by a highly experienced thyroid surgeon with a significant case volume (1,ØØØØ).
- The preferred surgical approach for pediatric patients is total thyroidectomy (1,ØØØO).
- Prior to surgery, it is crucial for pediatric patients with Graves' disease (GD) to achieve a state of biochemical euthyroidism. This may require pre-operative treatment with antithyroid drugs (ATDs), and if necessary, iodine, a beta-blocker, and glucocorticoid (1,ØØØØ).
- Administering pre-operative vitamin D treatment reduces the risk of transient post-operative hypocalcemia in those who are deficient in vitamin D (2,ØØOO).
- Initiation of levothyroxine treatment should commence shortly after thyroidectomy in pediatric patients (1,ØØOO).

Management of pediatric Graves' orbitopathy

- Children displaying eye-related symptoms should seek consultation with an orbital specialist, preferably within combined thyroid eye clinics staffed by both ophthalmologists and physicians (1,ØØØO).

- Mild symptoms of Graves' orbitopathy (GO) lacking inflammatory features can either be observed over time or, when deemed necessary, managed with selenium supplementation (2,ØØOO).
- In the rare instances of moderate to severe active GO cases, treatment options may include anti-inflammatory medications, such as intravenous corticosteroids (1,ØØOO).
- Chronic, stable, and inactive GO cases, which can adversely affect the patient's quality of life, can be considered for surgical interventions similar to those in adults. However, except for decompression surgery, these surgical procedures should be postponed until the facial skull has reached full growth (1,ØØOO).

Management of an increased thyroid cancer risk

- Similar to adults, young patients diagnosed with Graves' disease (GD) may face a slightly elevated risk of developing differentiated thyroid cancer (2,ØØOO).
- Children and adolescents with GD who present with a detectable thyroid nodule should receive care from a pediatric endocrinologist working in conjunction with a relevant multidisciplinary team (2,ØOOO).
- Young patients with a thyroid nodule or nodules should undergo either a thyroid ultrasound examination followed by cytological evaluation if suggested by the sonographic findings or consider total thyroidectomy (2,ØØOO).

Prognosis

- Young individuals who are diagnosed with Graves' disease (GD) during childhood and receive treatment may experience a reduced quality of life compared to their healthy peers. It is important to be mindful of this potential impact and, when deemed necessary, implement suitable measures to address and improve their well-being (1,ØØOO).

1.2.2 French Consensus on the Treatment of Adult Graves’ Disease (2018)

This consensus statement on the treatment of adult Graves’ disease was published in the Annals of Endocrinology (Paris) in December 2018[5].

Table 6. Levels of Evidence and Definitions

Level of Evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs with a high risk of bias
2++	• High quality systematic reviews of case-control or cohort studies • High quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

- The decision regarding the treatment for Graves' disease should be a collaborative process involving the patient. After providing a thorough explanation of the advantages and disadvantages of the three traditional treatment options, it is essential to seek the guidance of a specialist. They will help select the most suitable treatment and establish a monitoring plan (1/++).
- Regardless of the selected treatment approach, an appropriately adjusted dosage of antithyroid drugs should be prescribed initially to achieve a state of euthyroidism (1/++).

Antithyroid drugs in the treatment of Graves’ disease

- To manage hyperthyroidism, thiamazole and carbimazole are preferred over propylthiouracil, except during the first trimester of pregnancy or if there are plans for pregnancy (1/++).
- Regarding antithyroid drugs, there is a lack of strong evidence supporting or opposing the routine monitoring of blood counts during treatment. However, if blood-count monitoring is initiated, it is advisable to commence with a pre-treatment blood count (2/++).

- In the event of symptoms of infection or the onset of pharyngitis during antithyroid drug treatment, an immediate blood count should be conducted. If the polymorphonuclear neutrophil count falls below 800/mm3, it necessitates discontinuation of antithyroid treatment and definitively prohibits the reintroduction of thionamides (1/+++).
- Due to the risk of severe hepatitis, propylthiouracil (PTU) should be reserved for specific cases, including pregnancy or plans for pregnancy, minor thiamazole allergy, and situations involving iodine overload. There is no strong evidence either in favor of or against routine monitoring of transaminase levels. However, if clinical and/or severe hepatitis occurs (with transaminase levels exceeding 3 times the upper normal limit), it necessitates discontinuation of antithyroid treatment (1/++).
- There is limited strong evidence supporting the routine monitoring of anti-neutrophil antibodies. (2/+).
- Patients should receive comprehensive information, preferably in written form, regarding potential minor and major side effects of antithyroid treatment, as well as the initial symptoms to watch for and the appropriate steps to take if these symptoms arise. (1/++).
- The initial dosage of antithyroid drugs should be tailored to the severity of hyperthyroidism. The recommended starting doses are as follows: 40 mg daily for carbimazole and 30 mg daily for thiamazole if the FT4 concentration exceeds 3–4 times the upper limit of normal. For lower FT4 concentrations, initial doses should be 20–30 mg of carbimazole or 15–20 mg of thiamazole (1/++).
- Both the "adapted" and "combined" treatment protocols demonstrate equal efficacy. The decision regarding which protocol to choose is left to the clinician, who should consider their usual practice and take into account the patient's preference (No recommendations. No evidence in favor of one or other protocol)
- Regardless of the chosen treatment protocol, the standard duration of treatment is typically 12–18 months (1/++).
- During the euthyroid recovery phase, hormonal monitoring of antithyroid treatment primarily involves assessing FT4 ± FT3 levels. This monitoring should occur at least monthly until the patient reaches a state of euthyroidism, defined as the normalization of FT4 ± FT3 levels. It's important to note that TSH may remain below the normal range for one month or more even after thyroid function has normalized, so it serves as a secondary indicator of euthyroid status (1/++).

- After achieving euthyroid status and the normalization of TSH levels, hormonal monitoring of antithyroid treatment should include TSH and FT4 assessments at appropriate intervals. For adapted dose treatment, monitoring should occur at least every 2 months, while for combined treatment, it should be conducted every 4 months. The intervals can be adjusted if there are changes in the dosage or if results are unstable (1/++).
- At the conclusion of the standard treatment course, it is advisable to conduct an Anti-thyroid stimulating hormone receptor (anti-TSH-R) antibody assay to evaluate the risk of recurrence following treatment (1/++).

Role of β-blockers

- If hyperthyroidism reoccurs after discontinuation of antithyroid drug treatment, the treatment choices (such as a second course of traditional antithyroid drugs or more definitive approaches like radioiodine therapy or surgery) should be reevaluated through discussion with the patient, considering the clinical information. In specific situations, the option of extended-duration, low-dose antithyroid drug treatment may also be considered (2/+).
- In elderly patients experiencing symptomatic hyperthyroidism and in any patient with a resting heart rate exceeding 90–100 beats per minute, beta-blockers can be employed if there are no contraindications. Additionally, they can be considered for symptom relief in all individuals with symptoms related to hyperthyroidism (1/++).

Radioiodine administration in Graves' hyperthyroidism

- Prior to administering radioiodine, it is advisable to initiate beta-blocker treatment systematically in individuals with symptomatic hyperthyroidism. This precaution is taken due to the potential risk of transient exacerbation of hyperthyroidism following radioiodine treatment, especially when antithyroid drugs are contraindicated or not well tolerated (1/++).
- Medical preparation using antithyroid drugs can be beneficial when it is not contraindicated or not well tolerated, particularly in fragile patients (such as the elderly, those with severe symptoms, those with elevated thyroid hormone levels, or those with a cardiovascular history). If prescribed, antithyroid treatment should be temporarily discontinued for a period of 3–7 days surrounding the radioiodine treatment. However, there is no consensus on the optimal duration for this interruption (2/++).

- In the case of Graves' disease, an "ablative" approach is more suitable than a "dose-adjustment" approach when using radioiodine therapy. The radioiodine dose administered should be sufficient to induce hypothyroidism (1/++).
- There is no preference for a specific method to determine the radioiodine dose; both fixed and dose-adjusted methods can be employed. However, fixed or semi-fixed dose methods are advantageous due to their simplicity. (No specific recommendation; no grading provided).
- Regardless of the chosen dose determination method, it is essential to conduct thyroid ultrasound and scintigraphy imaging assessments. Ultrasound is used to characterize any nodules and measure thyroid volume. Scintigraphy, utilizing iodine-123 or technetium-99m, measures thyroid uptake under the same conditions as the actual treatment, with the potential interruption of antithyroid drugs if necessary (1/++).
- In women of child-bearing age, a pregnancy test should be conducted no later than 72 hours before administering iodine-131 treatment (1/++).
- Breastfeeding should be permanently discontinued at least 4 weeks before undergoing treatment (1/++).
- Following treatment, effective contraception should be maintained for a duration of 6 months (1/++).
- After ablative radioiodine treatment, it is recommended to measure TSH and FT4 levels at 4 weeks post-treatment and subsequently every 4–6 weeks for a total duration of 6 months. Specialist consultation during this period is essential to ensure appropriate hormone replacement therapy and prevent complications related to severe hypothyroidism. Additionally, during this consultation, the orbital status can be assessed (1/+++).
- Once hormonal balance has been successfully restored, it is necessary to undergo an annual TSH assay, with no specified time limit for its continuation (1/+++).
- Treatment failure is characterized by the presence of persistent hyperthyroidism 6–12 months following radioiodine treatment (1/+++).
- In the event of treatment failure, a second treatment may be considered, with the precaution of avoiding excessively low doses, which should not be less than 5–10 mCi or 185–370 MBq (2/++).

Radioiodine and orbitopathy

- Radioiodine treatment carries a risk of exacerbating pre-existing orbitopathy or inducing new orbitopathy, particularly in individuals who smoke. While radioiodine is not strictly contraindicated for individuals with orbitopathy, its

use should be limited to cases of mild or moderately inactive orbitopathy. Specific precautions should be taken, including patient education, strong encouragement to cease smoking, consultation with an ophthalmology specialist, oral corticosteroid therapy, and vigilant monitoring to prevent the development of hypothyroidism (1/+++).

- There is a lack of evidence supporting routine levothyroxine replacement therapy following treatment in patients with risk factors such as smoking or high TSH-R antibody levels but without orbitopathy.
- In individuals at a high risk of orbitopathy or those with mild or inactive orbitopathy, thyroid function should be evaluated through free T4 and TSH measurements within 2 weeks of receiving radioiodine treatment (1/++).

Radioiodine and nodules

- Before undergoing radioiodine treatment, it is recommended to conduct fine-needle aspiration in any thyroid nodule larger than 1 cm and those deemed suspicious based on ultrasound findings (1/+++).
- Radioiodine treatment may also be considered for cytologically benign nodules (1/++).
- Follow-up procedures should be similar to those typically conducted for thyroid nodules (1/++).

Surgical treatment in Graves’ disease

- Surgery is not the initial treatment of choice for Graves' disease (1/+).
- Surgery is recommended when medical treatment fails or when complications arise (2/+).
- Surgery should be carried out when the patient is in a euthyroid state (1/++).
- Surgery should be conducted in a specialized center or a center with extensive experience in thyroid surgery (1/++).
- Total thyroidectomy is the preferred initial approach (1/+).
- Alternatively, if the dissection of the first thyroid lobe is challenging, subtotal thyroidectomy can be considered with the aim of reducing the risk to recurrent nerves and parathyroid glands (2/+).
- There are no specific recommendations for the preoperative application of Lugol's iodine to reduce complication rates (2/+).
- The use of Lugol's iodine is at the discretion of the surgeon (2/+).

1.2.3 French Consensus on Graves' Disease and Pregnancy (2018)

Similarly to the consensus statement detailed in the section above, recommendations were also published on the management of Graves' disease in pregnancy[7].

Differential diagnoses in Graves' disease

- It is important to maintain normal thyroid parameter values according to the trimester of pregnancy and reference values established for pregnancy (1/+++).
- The diagnosis of hyperthyroidism during pregnancy should rely on TSH and free T4 measurements, with interpretation considering the normal physiological changes that occur during pregnancy (1/+++).
- The diagnosis of Graves' disease should be based on the assessment of anti-TSH-R antibodies (1/+++).
- In cases of hyperemesis gravidarum, it is necessary to evaluate thyroid function through TSH and free T4 measurements to assess thyroid dysfunction (1/++).
- Thyroid scintigraphy is not recommended during pregnancy due to contraindications (1/++).

Maternal complications of hyperthyroidism during pregnancy

- When maternal hyperthyroidism is confirmed, characterized by an elevated free T4 concentration, it should be treated and corrected (1/+++).
- The treatment of subclinical hyperthyroidism, which is defined as isolated low TSH concentration, is not recommended (1/+++).

Choice of treatment

- Treatment of Graves' disease during pregnancy primarily involves the use of antithyroid drugs. Levothyroxine, due to its limited placental transfer, is recommended using the adapted-dose strategy. If combined treatment (levothyroxine and antithyroid drugs) was employed before pregnancy, it's essential to discontinue levothyroxine and continue with antithyroid drugs at the adapted dose (1/+++).
- There have been reports of malformations associated with in utero exposure to imidazole-derivative antithyroid drugs and, to a lesser extent, propylthiouracil. Propylthiouracil is also associated with rare but severe cases of hepatitis. Therefore, it is recommended to prescribe propylthiouracil during the first trimester of pregnancy and then switch to an imidazole-derivative.

However, switching during pregnancy can disrupt thyroid balance and requires closer monitoring. If significant improvement in hyperthyroidism allows for dose reduction or discontinuation of antithyroid drugs during pregnancy, continuing propylthiouracil may be considered (1/++).

- If there is a switch of antithyroid drugs during pregnancy, thyroid monitoring should be intensified (1/++).
- Surgery is an option when there is an allergy to antithyroid drugs or when maternal hyperthyroidism is poorly controlled. Surgery is preferably performed during the second trimester (1/++).
- Radioiodine therapy is contraindicated during pregnancy (1/++).

Monitoring of antithyroid treatment

- Treatment of Graves' disease during pregnancy should adhere to the adapted-dose strategy (1/++).
- Monitoring of antithyroid treatment during pregnancy should be rigorous, with assessments initially conducted every 2 weeks and then every 2–4 weeks depending on the progression (1/++).
- Monitoring of antithyroid treatment during pregnancy relies on free T4 and TSH assays. TSH levels may remain low, while free T4 levels should be maintained in the upper range of normal (1/++).
- If, at the minimum antithyroid dose, the clinical condition is satisfactory and maternal free T4 levels decrease in two successive assays, discontinuation of treatment may be considered (2/++).
- Although there is no conclusive evidence, it is recommended to monitor transaminase levels every 2–4 weeks during propylthiouracil treatment during pregnancy. Patients should be advised to avoid other hepatotoxic drugs and to seek medical attention in case of digestive symptoms (2/+).

Pregnancy preparation

- Women of child-bearing age who have Graves' disease should receive information about the fetal risks associated with the condition and the management of hyperthyroidism during pregnancy (1/+++).
- Pregnancy should be avoided for at least 6 months following radioiodine therapy (1/++).
- In cases where radical therapy is being considered and there is a pregnancy plan, total thyroidectomy may be a preferable option over radioiodine

treatment because it leads to a faster decrease in anti-TSH-R antibody levels (2/++).

Fetal complications

- Fetuses of mothers with Graves' disease can potentially develop hyperthyroidism due to the passage of anti-TSH-R antibodies across the placenta, or hypothyroidism due to the passage of antithyroid drugs (1/++).
- The presence of a goiter in the fetus is the most effective sign of fetal thyroid dysfunction and can be detected through standardized ultrasound measurements based on gestational age (1/+++).
- Fetal hyperthyroidism may be suspected when there are signs such as fetal goiter, delayed intrauterine growth, and fetal tachycardia (which is a late sign of severe hyperthyroidism) (1/++).
- The goal of treatment is to prevent fetal hyperthyroidism through early detection of fetal thyroid hypertrophy and appropriate adjustment of maternal treatment. Additionally, the aim is to prevent fetal hypothyroidism resulting from antithyroid drug overdose or unjustified combination with levothyroxine. (The combination of maternal treatments is contraindicated.) (1/++).
- Effective treatment of fetal thyroid dysfunction is crucial to prevent premature mortality and long-term neurological complications (1/+++).

Monitoring: TRABs and risk threshold; biologic activity; ultrasound; indication of percutaneous umbilical blood sampling

- Anti-TSH-R antibody testing should be conducted at the beginning of pregnancy, and if these antibodies are present, monitoring should be intensified (1/+++).
- If the concentration of anti-TSH-R antibodies is > 5 IU/L as per the 2nd generation assay in the 2nd trimester, it indicates a risk of fetal and neonatal hyperthyroidism. In such cases, ultrasound monitoring should be intensified, with monthly fetal ultrasounds starting from 22 weeks' amenorrhea. The monitoring frequency should be adjusted based on the appearance of fetal thyroid hypertrophy (1/++).
- Because the quality of fetal thyroid ultrasound scans depends on the operator, it is advisable for both the mother and fetus to be monitored in a multidisciplinary expert center (1/++).
- Fetal goiter is defined by dimensions that exceed the 95th percentile based on gestational age (1/+++).

- Fetal blood sampling should only be considered in cases of fetal goiter when non-invasive assessments or treatment adjustments fail to determine fetal thyroid functional status. The decision to proceed with fetal blood sampling should be confirmed by a multidisciplinary prenatal diagnostic center (1/++).

Indications and treatment modalities (intra-amniotic levothyroxine injection, fetus-targeting maternal antithyroid drugs)

- Prenatal treatment has been found effective in correcting fetal and neonatal thyroid dysfunction.
- In cases of fetal hypothyroidism due to maternal antithyroid therapy, the maternal dose of antithyroid drugs should be reduced (1/++).
- For persistent hypothyroidism in the fetus despite appropriate maternal treatment, intra-amniotic administration of levothyroxine may be considered. This decision should follow confirmation by fetal blood sampling, which needs validation by a multidisciplinary prenatal diagnostic center (2/+).
- Fetal hyperthyroidism is managed through maternal antithyroid therapy (1/+).

Progression of children of mothers with Graves' disease

- In cases where anti-TSH-R antibodies are present during pregnancy, there is a risk of neonatal hyperthyroidism, particularly when antibody levels exceed 5 IU/L on the 2nd generation assay (1/+++).
- Umbilical blood should be systematically tested for TSH, free T4, and anti-TSH-R antibodies if the mother has anti-TSH-R antibodies or is on antithyroid drugs during pregnancy. These tests provide information about the prenatal status and/or treatment and guide postnatal monitoring (1/++).
- Neonatal hyperthyroidism is not a risk when anti-TSH-R antibodies were absent in the mother throughout pregnancy (1/++).
- High levels of anti-TSH-R antibodies in umbilical blood are associated with a significant risk of neonatal hyperthyroidism. Monitoring should continue, involving collaboration with a pediatric endocrinologist (1/++).
- Normal thyroid hormone levels (TSH and free T4) in umbilical blood at delivery do not predict neonatal hyperthyroidism (1/++).
- A rapid increase in free T4 levels beyond the age-related upper limit of normal between umbilical sampling and 3-5 days after birth is indicative of neonatal hyperthyroidism (1/++).

- Carbimazole treatment should be initiated at a dose of 0.5 mg/kg/day when biological signs of neonatal hyperthyroidism are observed, considering age-related normal values. Propranolol may be added if there are clinical signs.
- In cases of neonatal hyperthyroidism, carbimazole treatment should be continued until anti-TSH-R antibodies become negative (1/++).
- Low free T4 levels at birth, accompanied by low or non-elevated TSH levels, require monitoring in collaboration with a pediatric endocrinologist (2/++).
- There is inadequate evidence to suggest that maternal hyperthyroidism during pregnancy has any significant impact on the intellectual, psychological, or behavioral development of children and young adults (1/++).
- Currently, it is advisable to maintain free T4 levels within the normal range in women receiving treatment for Graves' disease during pregnancy (1, and expert opinion / ++).

1.2.4 European Group on Graves' Orbitopathy (EUGOGO) Clinical Practice Guidelines for the Medical Management of Graves' Orbitopathy (2021)

After the publication of the 2016 European Thyroid Association (ETA)/European Group on Graves's Orbitopathy (EUGOGO) guidelines for the management of Graves's orbitopathy (GO), several relevant studies have been published, particularly randomized clinical trials of newer biological agents for the treatment of moderate-to-severe and active GO. This prompted the EUGOGO Executive Committee to appoint an *ad hoc* task force committed to updating the guidelines, focusing on the medical management of GO[9].

Table 7. Quality of Evidence Recommendations as Defined by GRADE

Quality of Evidence	
Level 'ØØØØ'	High
Level 'ØØØO'	Moderate
Level 'ØØOO'	Low
Level 'ØOOO'	Very low

Table 8. Grading Scheme for Recommendations

Grading Scheme for Recommendations	
a	Strong recommendation: 'we recommend'
b	Weak recommendation: 'we suggest'

- Evaluate GO according to standardized criteria, categorizing it as active or inactive, and mild, moderate-to-severe, or sight-threatening. Include the assessment of quality of life using the GO-QoL questionnaire (1, ØØØO).
- Primary-care physicians, general practitioners, general internists, and specialists should refer patients with overt GO and mild cases at risk of deterioration (such as clinically active GO, smokers, severe/unstable hyperthyroidism, high serum TSHR-Ab titers) to combined thyroid-eye clinics or specialized centers with expertise in both endocrinology and ophthalmology. This will lead to accurate diagnosis and improved prognosis and quality of life (1, ØØOO).
- Physicians should advise all patients with Graves' hyperthyroidism, regardless of the presence of GO, to quit smoking (1, ØØØØ).
- Restore and maintain euthyroidism promptly in all patients with GO (1, ØØØØ).
- Provide oral prednisone/prednisolone prophylaxis to RAI-treated patients at risk of GO progression or development (e.g., smokers, severe/unstable hyperthyroidism, high serum TSHR-Ab). Regimen depends on risk level. Patients with longstanding and stably inactive GO can receive RAI without prednisone/prednisolone cover if risk factors for GO progression are absent. Avoid uncontrolled post-RAI hypothyroidism (1, ØØØØ).

Table 9. Classification of Severity of Graves' Orbitopathy. Adapted from the 2021 EUGOGO Guidelines.

Classification	Features
Mild	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	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)	Patients with dysthyroid optic neuropathy and/or corneal breakdown.

- If the impact of the disease on quality of life outweighs the risks, low-dose immunomodulatory therapy (for active GO) or rehabilitative surgery (for inactive GO) can be considered after thorough counseling and shared decision-making (2, ØØOO).

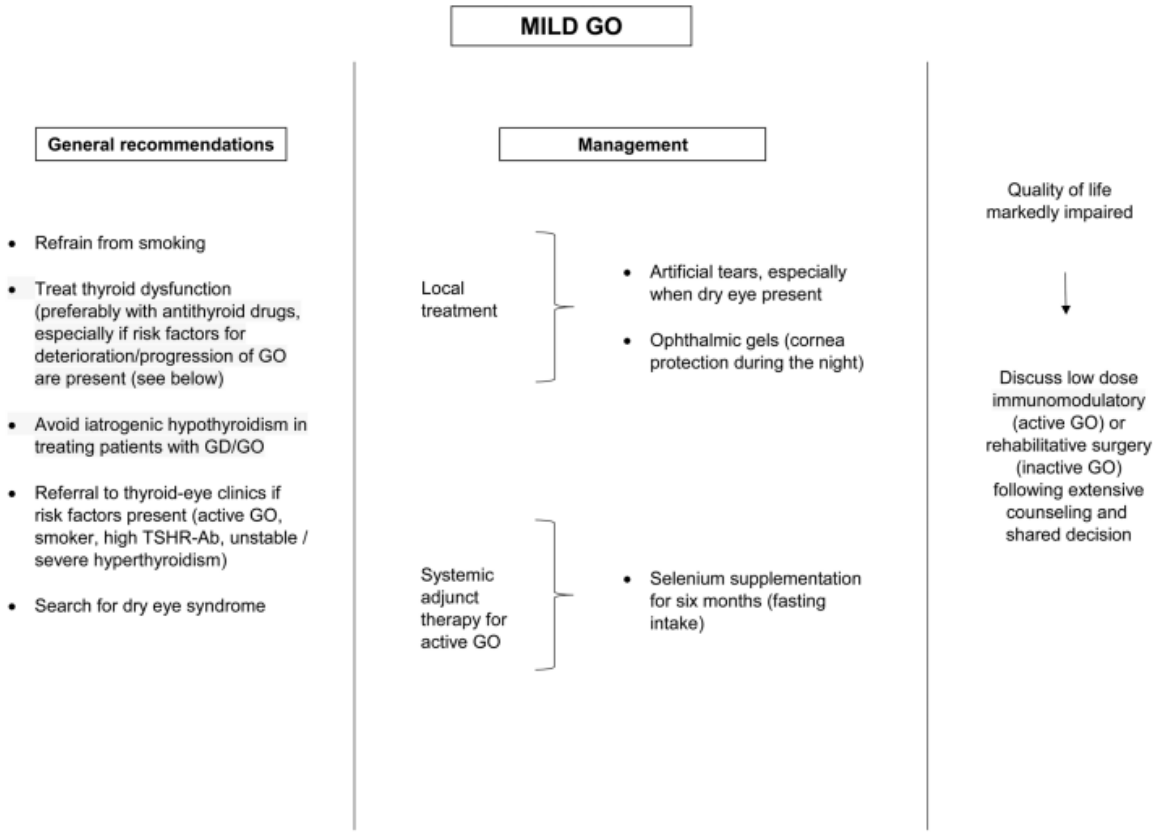

Figure 1. *Algorithm for the management of mild Graves' orbitopathy. Retrieved from the 2021 EUGOGO guidelines.*

- Provide extensive counseling to inform patients about the aims, expectations, benefits, and risks of different therapies. The selection of treatment should consider evidence-based effectiveness, safety, costs, health system

reimbursement, drug availability, treatment facilities, and the patient's informed choice within a shared decision-making process (1, ØØOO).

- Limit the cumulative dose of i.v. glucocorticoids to a maximum of 8.0 g per cycle. Patients with recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity, or uncontrolled hypertension should not receive i.v. glucocorticoids. Ensure well-controlled diabetes before starting treatment and administer this treatment only in experienced centers capable of managing potential serious adverse events (1, ØØØO)
- In most cases of moderate-to-severe and active GO, an intermediate dose of intravenous glucocorticoids is recommended. This includes a starting dose of 0.5 g of intravenous methylprednisolone once weekly for 6 weeks, followed by 0.25 g once weekly for 6 weeks, resulting in a cumulative dose of 4.5 g (1, ØØØØ).
- A high-dose regimen of intravenous glucocorticoids is reserved for more severe cases within the moderate-to-severe and active GO spectrum. This regimen involves a starting dose of 0.75 g of intravenous methylprednisolone once weekly for 6 weeks, followed by 0.5 g once weekly for 6 weeks, resulting in a cumulative dose of 7.5 g (1, ØØØO).
- Clinicians should closely monitor individual patients receiving glucocorticoid therapy for treatment response and adverse events. If the side effects of glucocorticoid treatment outweigh the benefits, clinicians should consider discontinuing glucocorticoid therapy in favor of an alternative approach or vigilant monitoring (2, ØØOO).
- Mycophenolate demonstrates a favorable efficacy/safety profile in patients with moderate-to-severe and active GO, either as monotherapy or in combination with intravenous glucocorticoids (1, ØØØØ).
- Orbital radiotherapy is considered an effective second-line treatment for moderate-to-severe and active GO, especially when combined with glucocorticoids, particularly in the presence of diplopia and/or restriction of extraocular motility (1, ØØØO).
- The combination of cyclosporine and oral glucocorticoids is a valid second-line treatment for moderate-to-severe and active GO (1, ØØØØ).
- Consideration may be given to azathioprine as a second-line and glucocorticoid-sparing agent in combination with oral glucocorticoids (1, ØØOO).
- Teprotumumab is a very promising drug with a strong reduction in exophthalmos, diplopia, and improvement in quality of life. It is currently considered a second-line option, pending longer-term data, availability,

affordability, costs, and the need for subsequent rehabilitative surgery (1, ØØØO).

- Rituximab can be considered a second-line treatment for patients with moderate-to-severe and active GO of recent onset (<12 months) if refractory to intravenous glucocorticoids, with the exclusion of dysthyroid optic neuropathy (DON). This treatment should be administered in experienced centers capable of managing potentially serious adverse events (1, ØØOO).
- The first-line treatment for moderate-to-severe and active GO consists of intravenous methylprednisolone in combination with oral mycophenolate sodium (or mofetil) (1, ØØØO).

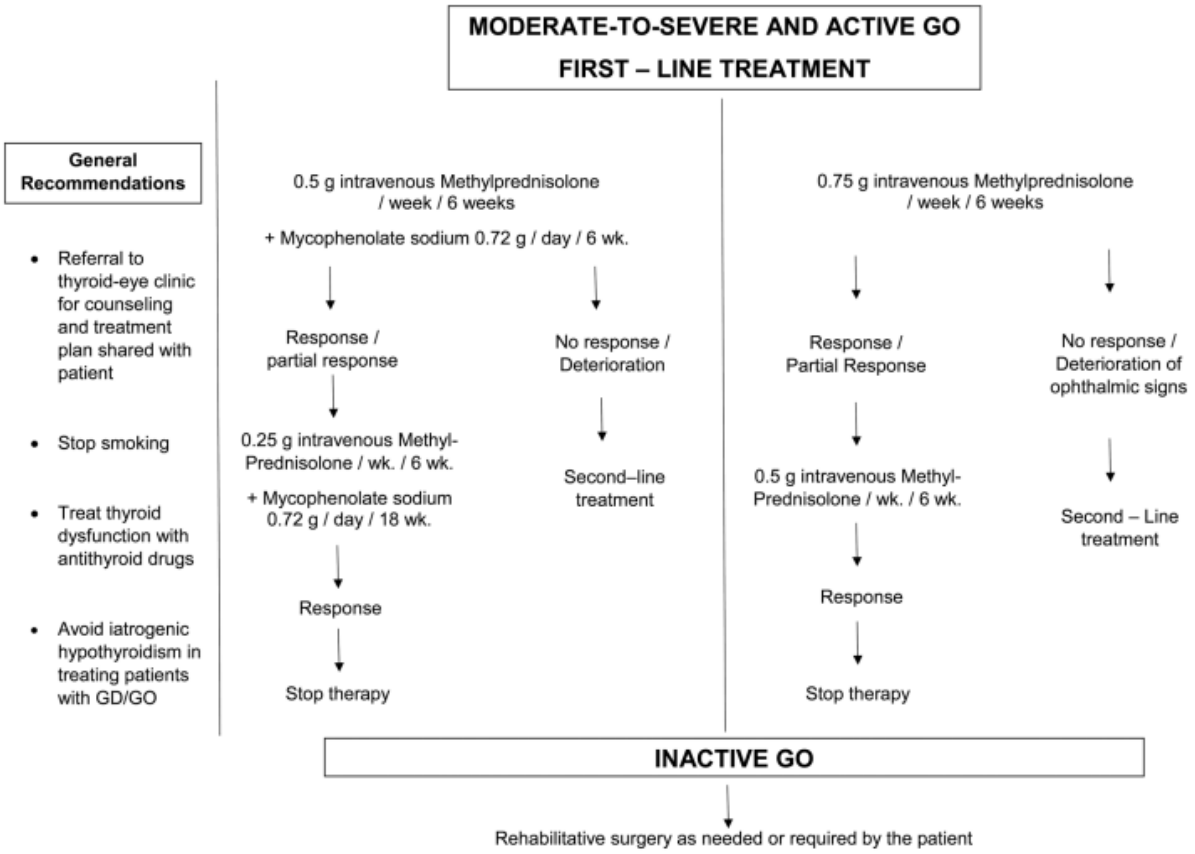

Figure 2. *Algorithm for the first-line management of moderate-to-severe and active Graves' orbitopathy. Retrieved from the 2021 EUGOGO guidelines.*

- In more severe forms of moderate-to-severe and active GO, including constant/inconstant diplopia, severe inflammatory signs, and exophthalmos > 25 mm, intravenous methylprednisolone at the highest cumulative dose (7.5 g per cycle) as monotherapy represents an additional valid first-line treatment (1, ØØØO).

- If the response to primary treatment is inadequate, and GO remains at a moderate-to-severe and active stage, considering the following second-line treatments is recommended:
    a. A second course of intravenous methylprednisolone monotherapy, commencing with high single doses (0.75 g) and a maximum cumulative dose of 8 g per cycle.
    b. Combining oral prednisone/prednisolone with either cyclosporine or azathioprine.
    c. Employing orbital radiotherapy in conjunction with oral or intravenous glucocorticoids.
    d. Considering the use of Teprotumumab, Rituximab, or Tocilizumab (1, ØØØO).
- Although based solely on expert opinion due to the lack of randomized trials, the task force suggests that combining orbital radiotherapy with intravenous methylprednisolone is a potential second-line treatment for moderate-to-severe and active GO (2, ØØOO).

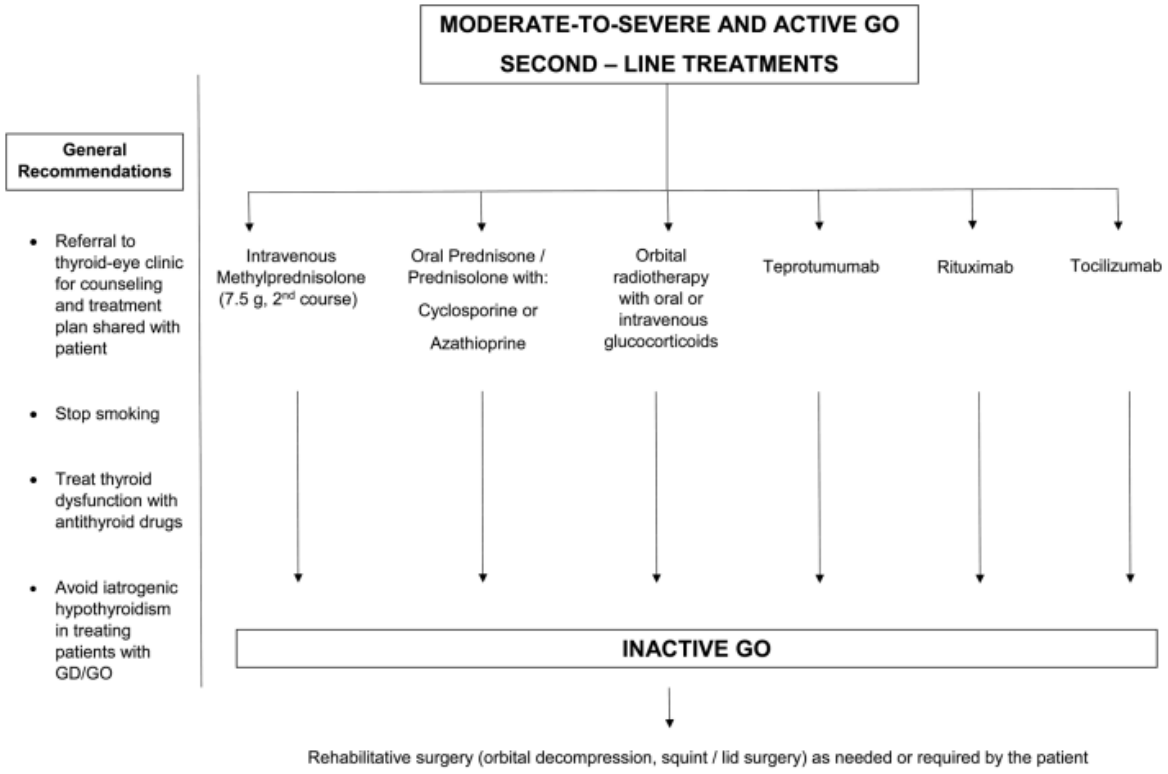

Figure 3. *Algorithm for the second-line management of moderate-to-severe and active Graves' orbitopathy. Retrieved from the 2021 EUGOGO guidelines.*

- For patients with mild and inactive GO, any treatment for hyperthyroidism can be utilized based on standardized criteria and patient preference (1, ØØOO).

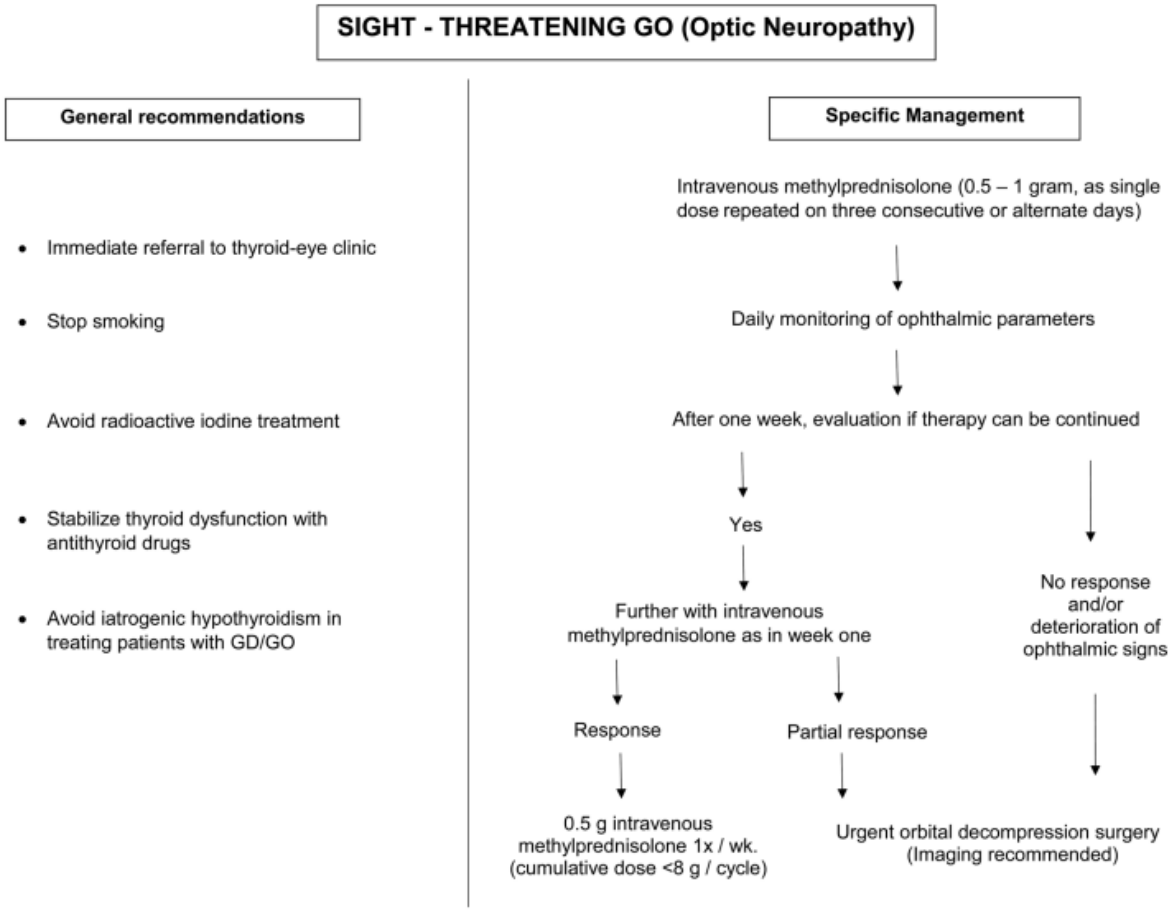

Figure 4*. Algorithm for the management of sight-threatening Graves' orbitopathy. Retrieved from the 2021 EUGOGO guidelines.*

- In cases of mild and active GO, the preferred options are antithyroid drugs (ATDs) or thyroidectomy. If radioactive iodine (RAI) treatment is chosen, prophylaxis with prednisone/prednisolone should be considered (1, ØØØO).
- Similar to mild and inactive GO, thyroid treatment can follow standardized criteria and patient choice. However, in cases where RAI treatment is selected, consideration should be given to prednisone/prednisolone prophylaxis if risk factors (e.g., smoking, high TSHR-Ab) are present (1, ØØOO).
- In cases of moderate-to-severe and active GO, the primary focus should be on treating hyperthyroidism with ATDs until the treatment of GO is completed (1, ØØØO).

- In emergencies involving sight-threatening GO, the absolute priority is to treat GO. Hyperthyroidism should also be managed with ATDs until the treatment of GO is concluded (1, ØØØO).

1.2.5 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum (2017)

The aim of these guidelines published in 2017 by the American Thyroid Association is to inform clinicians, patients, researchers, and health policy makers on published evidence relating to the diagnosis and management of thyroid disease in women during pregnancy, preconception, and the postpartum period[10].

Table 10. Recommendations (for Therapeutic Interventions) Based on Strength of Evidence

Recommendation and evidence quality	Description of supporting evidence	Interpretation
Strong recommendation		
High-quality evidence	RCT without important limitations or overwhelming evidence from observational studies	Can apply to most patients in most circumstances without reservation
Moderate-quality evidence	RCT with important limitations or strong evidence from observational studies	Can apply to most patients in most circumstances without reservation
Low-quality evidence	Observational studies/case studies	May change when higher-quality evidence becomes available
Weak recommendation		
High-quality evidence	RCT without important limitations or overwhelming evidence from observational studies	Best action may differ based on circumstances or patients' values
Moderate-quality evidence	RCT with important limitations or strong evidence from observational studies	Best action may differ based on circumstances or patients' values

Low-quality evidence	Observational studies/case studies	Other alternatives may be equally reasonable
Insufficient	Evidence is conflicting, of poor quality, or lacking	Insufficient evidence to recommend for or against

Table 11. Recommendations (for Diagnostic Interventions) Based on Strength of Evidence

Recommendation and evidence quality	Description of supporting evidence	Interpretation
Strong recommendation		
High-quality evidence	Evidence from one or more well-designed nonrandomized diagnostic accuracy studies (i.e., observational—cross-sectional or cohort) or systematic reviews/meta-analyses of such observational studies (with no concern about internal validity or external generalizability of the results).	Implies the test can be offered to most patients in most applicable circumstances without reservation.
Moderate-quality evidence	Evidence from nonrandomized diagnostic accuracystudies (cross-sectional or cohort), with one or more possible limitations causing minor concern about internal validity or external generalizability of the results.	Implies the test can be offered to most patients in most applicable circumstances without reservation.
Low-quality evidence	Evidence from nonrandomized diagnostic accuracy studies with one or more important limitations causing serious concern about internal validity or external generalizability of the results.	Implies the test can be offered to most patients in most applicable circumstances, but the utilization of the test may change when higher-quality evidence becomes available.
Weak recommendation		

High-quality evidence	Evidence from one or more well-designed nonrandomized diagnostic accuracy studies (i.e., observational—cross-sectional or cohort) or systematic reviews/meta-analyses of such observational studies (with no concern about internal validity or external generalizability of the results).	The degree to which the diagnostic test is seriously considered may differ depending on circumstances or patients 'or societal values.
Moderate-quality evidence	Evidence from nonrandomized diagnostic accuracy studies (cross-sectional or cohort), with one or more possible limitations causing minor concern about internal validity or external generalizability of the results.	The degree to which the diagnostic test is seriously considered may differ depending on individual patients'/practice circumstances or patients 'or societal values.
Low-quality evidence	Evidence from nonrandomized diagnostic accuracy studies with one or more important limitations causing serious concern about internal validity or external generalizability of the results.	Alternative options may be equally reasonable.
Insufficient	Evidence may be of such poor quality, conflicting, lacking (i.e., studies not done), or not externally generalizable to the target clinical population such that the estimate of the true effect of the test is uncertain and does not permit a reasonable conclusion to be made.	Insufficient evidence exists to recommend for or against routinely offering the diagnostic test.

Thyrotoxicosis in Pregnancy

- If a suppressed serum TSH level is identified during the first trimester (TSH lower than the reference range), it is recommended to conduct a thorough medical history, physical examination, and measure maternal serum FT4 or TT4 concentrations. In certain cases, measuring TRAb (thyroid receptor antibodies) and maternal TT3 (total triiodothyronine) levels may be beneficial in determining the cause of thyrotoxicosis (Strong recommendation, moderate-quality evidence).
- Radionuclide scintigraphy or radioiodine uptake measurements should be avoided during pregnancy (Strong recommendation, high-quality evidence).
- The appropriate management of abnormal maternal thy-roid tests attributable to gestational transient thyrotoxicosis and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed. ATDs are not recommended, though b-blockers may be considered (Strong recommendation, moderate-quality evidence).

Table 12. Advantages and Disadvantages of Therapeutic Options for Women with Graves' Disease Seeking Future Pregnancy. Adapted from the 2017 ATA Guideline.

Therapy	Advantages	Disadvantages
Antithyroid drugs	Effective treatment to euthyroid state within 1-2 months. Often induces gradual remission of autoimmunity (decreasing antibody titers). Easily discontinued or modified. Treatment is easy to take. Relatively inexpensive.	Medication adverse effects (mild 5-8%; severe 02%). Birth defects associated with use during pregnancy (MMI 3-4%; PTU 2-3% though less severe). Relapse after drug withdrawal likely in 50-70%.
Radioactive iodine	Easy oral administration. Reduction in goiter size. Future relapse of hyperthyroidism very rare.	Repeat therapy at times necessary. Rising antibody titers following treatment may contribute to worsening orbitopathy or fetal risk.
Thyroidectomy	Definitive therapy of hyperthyroidism. Stable euthyroid state is easily	Life-long need for levothyroxine supplementation.

	achieved on re-placement levothyroxine therapy. Post surgery, gradual remission of autoimmunity occurs. Goiter disappears.	Surgical complications occur in 2-5%. Healing and recovery from surgery; permanent neck scar.

MMI: Methimazole; PTU: Propylthiouracil

- All women of childbearing age who experience thyrotoxicosis should engage in discussions about the potential for future pregnancy. Specifically, women with Graves' disease (GD) who plan to become pregnant should receive counseling regarding the challenges of managing the condition during pregnancy, including the potential risks of birth defects associated with the use of antithyroid drugs (ATDs). Preconception counseling should encompass a thorough review of the risks and advantages of various treatment options, as well as consideration of the patient's desired timing for conception (Strong recommendation, high-quality evidence).
- Women with thyrotoxicosis should aim to achieve a stable euthyroid state before attempting pregnancy. There are various treatment options available, each carrying its own set of advantages and disadvantages. These options include radioactive iodine (131I) ablation, surgical thyroidectomy, or antithyroid drug (ATD) therapy. It's important to carefully consider these treatment choices in light of their potential risks and benefits, particularly in the context of future pregnancy plans (Strong recommendation, moderate-quality evidence).

Management of patients with Graves’ hyperthyroidism during pregnancy

- Women who are taking either Methimazole (MMI) or Propylthiouracil (PTU) should be advised to promptly confirm the possibility of pregnancy as soon as they suspect it. If a pregnancy test yields a positive result, it is crucial for pregnant women to get in touch with their healthcare provider without delay to ensure appropriate management and guidance during pregnancy (Strong recommendation, high-quality evidence)
- In the case of a newly pregnant woman with Graves' disease (GD) who is currently on a low dose of either Methimazole (MMI) (≤5–10 mg/day) or Propylthiouracil (PTU) (≤100–200 mg/day), the healthcare provider should consider the possibility of discontinuing the antithyroid medication due to potential teratogenic effects. The decision to stop the medication should be based on various factors, including the patient's medical history, the size of the goiter, the duration of therapy, recent thyroid function test results,

measurement of TRAb (thyrotropin receptor antibodies), and other clinical considerations (Weak recommendation, low-quality evidence).

- Following the discontinuation of antithyroid medication, maternal thyroid function testing (including TSH, and FT4 or TT4) and clinical examinations should be conducted every 1–2 weeks to assess both maternal and fetal thyroid status. If the pregnant woman remains clinically and biochemically euthyroid, the testing intervals may be extended to 2–4 weeks during the second and third trimesters (Weak recommendation, low-quality evidence).
- At each assessment, the decision to continue conservative management (withholding antithyroid medication) should be made based on both the clinical and biochemical evaluation of maternal thyroid status (Weak recommendation, low-quality evidence).
- In pregnant women at high risk of developing thyrotoxicosis if antithyroid drugs were to be discontinued, it may be necessary to continue antithyroid medication. Factors that predict a high clinical risk include current hyperthyroidism or the need for >5–10 mg/day MMI or >100–200 mg/day PTU to maintain a euthyroid state. In such cases:
- Propylthiouracil (PTU) is strongly recommended for treating maternal hyperthyroidism through 16 weeks of pregnancy (Strong recommendation, moderate-quality evidence).
- Pregnant women who are receiving Methimazole (MMI) and require ongoing therapy during pregnancy should be switched to PTU as early as possible (Weak recommendation, low-quality evidence).
- When transitioning from MMI to PTU, a dose ratio of approximately 1:20 should be used (e.g., MMI 5 mg/day = PTU 50 mg twice daily) (Strong recommendation, moderate-quality evidence)
- If antithyroid drug therapy is needed after 16 weeks of gestation, it remains unclear whether PTU should be continued or if therapy should be changed to MMI. Both medications have potential adverse effects, and switching between them may result in a period of less tightly controlled thyroid function. Therefore, no specific recommendation regarding switching antithyroid drug medication can be made at this time (No recommendation, insufficient evidence).
- Pregnant women receiving antithyroid drugs (ATDs) should undergo regular monitoring of FT4/TT4 and TSH levels approximately every 4 weeks (Strong recommendation, moderate-quality evidence).
- During pregnancy, antithyroid medication should be prescribed at the minimal effective dosage of either Methimazole (MMI) or Propylthiouracil

(PTU), with the objective of maintaining maternal serum FT4/TT4 levels at or slightly above the upper limit of the reference range (Strong recommendation, high-quality evidence).

- The combination of levothyroxine (LT4) and ATD) should generally be avoided during pregnancy, except in rare cases of isolated fetal hyperthyroidism (Strong recommendation, high-quality evidence).

Thyroidectomy role in the management of GD during pregnancy

- Thyroidectomy during pregnancy may be necessary in specific situations. If deemed necessary, the best timing for thyroidectomy is typically during the second trimester of pregnancy. However, if the mother has a high concentration of TRAb (>3 times the upper reference limit for the assay), close monitoring of the fetus for the development of fetal hyperthyroidism should continue throughout the pregnancy, even if the mother's thyroid function is normal after thyroidectomy (Strong recommendation, high-quality evidence).
- We agree with the consensus guidelines from the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, as stated in 2011 and revised in 2015:
- A pregnant woman should never be denied necessary surgery, regardless of the trimester.
- Elective surgery should be postponed until after delivery.
- If feasible, non-urgent surgery should be scheduled during the second trimester of pregnancy when the risk of preterm contractions and spontaneous abortion is lower.
- In cases where a patient with Graves' disease requires urgent non-thyroid surgery and is well controlled on antithyroid drugs (ATDs), no additional preparation is typically needed. Beta-blockers may also be used if necessary (Strong recommendation, moderate-quality evidence)

TRAb levels testing

- If a pregnant woman has a previous history of Graves' disease treated with thyroid ablation (radioiodine or surgery), it is strongly advised to have a maternal blood test to check TRAb levels as part of the initial thyroid function assessment in early pregnancy. (Strong recommendation, moderate-quality evidence)
- If the initial TRAb test in early pregnancy shows elevated levels, it is strongly recommended to repeat the TRAb testing between weeks 18 and 22 of pregnancy (Strong recommendation, moderate-quality evidence).

- If the initial TRAb test in early pregnancy indicates undetectable or low TRAb levels, further TRAb testing is not necessary (Weak recommendation, moderate-quality evidence).
- If a patient is already taking antithyroid drugs (ATDs) to manage Graves' hyperthyroidism when pregnancy is confirmed, it is weakly recommended to perform a maternal blood test to measure TRAb levels (Weak recommendation, moderate-quality evidence).
- If the patient continues treatment with ATDs for Graves' disease up to mid-pregnancy, it is strongly recommended to repeat the TRAb test between weeks 18 and 22 (Strong recommendation, moderate-quality evidence).
- If elevated TRAb levels are detected between weeks 18 and 22 or if the mother is still taking ATDs in the third trimester, another TRAb measurement should be conducted in late pregnancy (between weeks 30 and 34). This is essential to assess the need for monitoring the newborn and postnatal care. (Strong recommendation, high-quality evidence).

Fetal monitoring

- Fetal monitoring is advisable for pregnant women with poorly managed hyperthyroidism in the latter half of pregnancy and for those who exhibit elevated TRAb levels at any point during pregnancy (exceeding three times the upper normal limit). It is recommended to consult with an experienced obstetrician or a specialist in maternal-fetal medicine for this purpose. The monitoring process may involve the use of ultrasound to evaluate fetal heart rate, growth, amniotic fluid levels, and the potential presence of fetal goiter. (Strong recommendation, moderate-quality evidence).
- Cordocentesis should only be employed in exceptional situations and should be conducted in a suitable medical environment. In some rare instances, when fetal goiter is identified in pregnant women undergoing ATD treatment, cordocentesis may be considered to assist in determining whether the fetus is experiencing hyperthyroidism or hypothyroidism (Weak recommendation, low-quality evidence).
- If ATD treatment is prescribed for hyperthyroidism resulting from autonomous nodules, it is crucial to closely observe the fetus for the development of goiter and signs of hypothyroidism in the latter half of pregnancy. A minimal ATD dose should be administered with the objective of maintaining the maternal FT4 or TT4 levels at or slightly above the upper limit of the reference range (Strong recommendation, low-quality evidence).

Lactating women with hyperthyroidism

- The effect of maternal hyperthyroidism on breastfeeding is not adequately understood. Consequently, there is no recommendation to treat maternal hyperthyroidism with the aim of enhancing lactation at this moment (No recommendation, insufficient evidence).
- The use of131I is not recommended during breastfeeding. If necessary, 123I can be utilized provided that breast milk is expressed and disposed of for 3–4 days before breastfeeding is resumed. Similarly, if Tc-99m pertechnetate is administered, it is necessary to pump and discard breast milk during the day of the testing procedure (Strong recommendation, moderate-quality evidence).
- The decision to treat hyperthyroidism in lactating women should be guided by the same principles applied to non-lactating women (Strong recommendation, low-quality evidence).
- When antithyroid medication is necessary for women who are breastfeeding, both MMI (up to a maximum dose of 20 mg/day) and PTU (up to a maximum dose of 450 mg/day) can be used. Since a small but measurable amount of both PTU and MMI can pass into breast milk, it is recommended to use the lowest effective dose of MMI/Carbimazole or PTU (Strong recommendation, moderate-quality evidence).
- Breastfed infants born to mothers receiving ATD treatment should undergo regular pediatric health check-ups to ensure proper growth and development. It is not necessary to routinely test the child's thyroid function (Weak recommendation, moderate-quality evidence)

Postpartum thyroiditis

- All patients with depression, including postpartum depression, should be screened for thyroid dysfunction (Strong recommendation, low-quality evidence).
- In the hyperthyroid phase of postpartum thyroiditis (PPT), symptomatic women can receive treatment with beta-blockers. A safe beta-blocker for lactating women, like propranolol or metoprolol, should be used at the lowest effective dose to relieve symptoms. This treatment is generally necessary for a few weeks (Strong recommendation, moderate-quality evidence).
- ATDs are not recommended for the treatment of the thyrotoxic phase of PPT (Strong recommendation, high-quality evidence)

- Following the resolution of the thyrotoxic phase of PPT, serum TSH should be measured in approximately 4–8weeks (or if new symptoms develop) to screen for the hypothyroid phase (Strong recommendation, high-quality evidence).

Screening in pregnant women

- There is not enough evidence to support or oppose the idea of screening all pregnant women for abnormal TSH levels in the early stages of pregnancy (No recommendation, insufficient evidence).
- There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations preconception, with the exception of women planning assisted reproduction or those known to have TPOAb positivity (No recommendation, insufficient evidence).
- All pregnant women should be verbally screened at the initial prenatal visit for any history of thyroid dysfunction, and prior or current use of either thyroid hormone (LT4) or antithyroid medications (MMI, CM, or PTU) (Strong recommendation, high-quality evidence).

1.2.6 Japan Thyroid Association/Japan Endocrine Society Guidelines for the Management of Thyroid Storm – First Edition (2016)

Based on the evidence obtained by nationwide surveys and additional literature searches, the clinical guidelines for the management of thyroid storm were developed. They include 15 recommendations for the treatment of thyrotoxicosis and organ failure in the central nervous system, cardiovascular system, and hepato-gastrointestinal tract, admission criteria for the intensive care unit, and prognostic evaluation. Preventive approaches to thyroid storm, roles of definitive therapy, and future prospective trial plans for the treatment of thyroid storm are also proposed[11].

Table 13. Quality of Evidence and Definitions

Quality of evidence	
High	Randomized controlled trials without important limitations, or overwhelming evidence from observational studies
Moderate	Randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies
Low	Observation studies or case series
Insufficient for grading	Evidence is conflicting, of poor quality, or lacking

Table 14. Strength of Recommendations and Definitions

Strength of recommendation	
Strong	Benefits clearly outweigh risks and burdens, or risks and burdens clearly outweigh benefits
Weak	Benefits closely balanced with risks and burdens
None	Balance of benefits and risks cannot be determined

Table 15. The Burch-Wartofsky Point Scale for Diagnosis of Thyroid Storm

Criteria	Points
Thermoregulatory dysfunction Temperature (°C)	
37.2-37.7	5
37.8-38.3	10
38.4-38.8	15
38.9-39.3	20
39.4-39.9	25
≥ 40.0	30
Cardiovascular Tachycardia (beats per minute)	
90-109	5
110-119	10
120-129	15
130-139	20
≥ 140	25
Atrial fibrillation	
Absent	0
Present	20
Congestive heart failure	
Absent	0
Mild	5
Moderate	10
Severe	15
Gastrointestinal-hepatic dysfunction Manifestation	

Absent	0
Moderate (diarrhea, abdominal pain, nausea/vomiting)	10
Severe (jaundice)	20
Central nervous system disturbance Manifestation	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, come)	30
Precipitating event Status	
Absent	0
Present	10
Total score	
≥ 45	Thyroid storm
25-44	Impending storm
< 25	Storm unlikely

Table 16. The Diagnostic Criteria for Thyroid Storm (TS) of the Japan Thyroid Association (Retrieved from the 2016 JTA/JES Guidelines).

Prerequisite for diagnosis		
Presence of thyrotoxicosis with elevated levels of free triiodothyronine (FT3) or free thyroxine (FT4)		
Symptoms		
1. Central nervous system (CNS) manifestations: Restlessness, delirium, mental aberration/psychosis, somnolence/lethargy, coma (≥1 on the Japan Coma Scale or ≤14 on the Glasgow Coma Scale)		
2. Fever : ≥ 38˚C		
3. Tachycardia : ≥ 130 beats per minute or heart rate ≥ 130 in atrial fibrillation		
4. Congestive heart failure (CHF) : Pulmonary edema, moist rales over more than half of the lung field, cardiogenic shock, or Class IV by the New York Heart Assciation or ≥ Class III in the Killip classification		
5. Gastrointestinal (GI)/hepatic manifestations : nausea , vomiting, diarrhea, or a total bilirubin level ≥ 3.0 mg/dL		
Diagnosis		
Grade of TS	Combinations of features	Requirements for diagnosis
TS1	First combination	Thyrotoxicosis and at least one CNS manifestation and fever, tachycardia, CHF, or GI/ hapatic manifestations
TS1	Alternate combination	Thyrotoxicosis and at least three combinations of fever, tachycardia, CHF, or GI/ hapatic manifestations
TS2	First combination	Thyrotoxicosis and a combination of two of the following: fever, tachycardia, CHF, or GI/hepatic manifastations
TS2	Alternate combination	Patients who met the diagnosis of TS1 except that serum FT3 or FT4 level are not available
Exclusion and provisions		
Cases are excluded if other underlying diseases clearly causing any of the following symptoms: fever (*e.g.*, pneumonia and malignant hyperthermia), impaired consciousness (*e.g.*, psychiatric disorders and cerebrovascular disease), heart failure (*e.g.*, acute myocardial infarction), and liver disorders (*e.g.*, viral hepatitis and acute liver failure). Therefore, it is difficult to determine whether the symptom is caused by TS or is simply a manifestation of an undelying disease; the symptom should be regarded as being due to a TS that is caused by these precipitating factors. Clinical judgment in this matter is required.		

TS1, "Definite" TS; TS2, "Suspected" TS.

- Thyroid storm is an urgent endocrine situation characterized by rapid deterioration occurring within days or even hours after initial presentation and is associated with a high mortality rate. While most instances of thyroid storm arise due to the presence of a precipitating factor in combination with an underlying thyroid condition, typically untreated or poorly managed Graves' disease, exceptionally rare cases can involve other hyperthyroid conditions such as destructive thyroiditis, toxic multinodular goiter, TSH-secreting pituitary adenoma, hCG-secreting hydatidiform mole, or metastatic thyroid cancer.
- To mitigate the effects of thyrotoxicosis on various organ systems, a multifaceted strategy involving antithyroid drugs (ATDs), inorganic iodide, corticosteroids, beta-adrenergic antagonists (beta-AAs), and antipyretic agents (Strength of recommendation: high, Quality of evidence: moderate)
- ATDs, either MMI or PTU, should be administered for the treatment of hyperthyroidism in thyroid storm (Strength of recommendation: high, Quality of evidence: low)

- Intravenous administration of MMI is recommended in severely ill patients with consciousness disturbances or impaired gastrointestinal tract function. (Strength of recommendation: high, Quality of evidence: low)
- In cases of thyroid storm resulting from hyperthyroid conditions, inorganic iodide should be administered in conjunction with antithyroid drugs (ATDs) (Strength of recommendation: high, Quality of evidence: moderate)
- Corticosteroids (300 mg/day hydrocortisone or 8 mg/day dexamethasone) should be administered to patients with thyroid storm regardless of its origin) Strength of recommendation: high, Quality of evidence: moderate)
- For individuals experiencing thyroid storm with elevated body temperature, proactive cooling should be initiated using acetaminophen along with physical cooling methods such as cooling blankets or ice packs (Strength of recommendation: high, Quality of evidence: moderate)
- Therapeutic plasmapheresis (TPE) may be contemplated if there is no observable clinical improvement within 24 to 48 hours following the initial treatment, which should include adequate doses of antithyroid drugs, inorganic iodine, corticosteroids, or beta-adrenergic antagonists, in addition to specific treatment for the underlying condition and complications associated with thyroid storm (Strength of recommendation: weak, Quality of evidence: low)
- Apart from promptly addressing thyrotoxicosis, it is essential to differentially diagnose and treat acute consciousness disturbances, psychosis, and seizures in cases of thyroid storm. This should be carried out following established guidelines and in consultation with a psychiatrist or neurologist (Strength of recommendation: strong, Quality of evidence: low)
- The preferred initial treatment for tachycardia in thyroid storm should be beta1-selective adrenergic antagonists (AAs) like landiolol, esmolol (administered intravenously), or bisoprolol (given orally). Other oral medications with beta1-selective activity are also considered suitable. While non-selective beta-AAs like propranolol are not contraindicated, they are not recommended for managing tachycardia in thyroid storm.
    1. In patients classified as Killip class ≤ III, if their heart rate is ≥150 bpm, the initial treatment choice should be either landiolol or esmolol. When the heart rate falls below 150 bpm, it's possible to switch to an oral beta1-selective medication.
    2. For patients in Killip class IV, the use of landiolol or esmolol may be considered if their heart rate is ≥150 bpm.

3. Landiolol should be initiated intravenously at a dose of 1 μg/kg/min, with appropriate dosage adjustments while monitoring the heart rate (in the range of 1–10 μg/kg/min). Esmolol should be started intravenously with a 1 mg/kg dose over 30 seconds, and its dosage should be adjusted as needed while monitoring the heart rate (approximately ~150 μg/kg/min). Bisoprolol is administered orally at a daily dose of 2.5–5 mg.
4. The heart rate should be controlled to ≤130 bpm when using beta-Adrenergic Antagonists (beta-AAs). Consider discontinuing beta-AAs if the heart rate falls below 80 bpm, systolic blood pressure is less than 80 mmHg, or the cardiac index is ≤2.2 L/min/m2.
5. Exercise caution when using landiolol or esmolol in patients with bronchial asthma and chronic obstructive pulmonary disease (COPD). Consider switching to verapamil or diltiazem if an asthma attack occurs (Strength of recommendation: high, Quality of evidence: low)

- When atrial fibrillation occurs:
    1. Digitalis is used in patients without severe renal dysfunction. It is given intravenously at an initial dose of 0.125 to 0.25 mg, followed by an appropriate maintenance dose with careful monitoring for signs and symptoms of digitalis toxicity.
    2. When there is a rapid deterioration of hemodynamics due to atrial fibrillation, it is advisable to perform cardioversion after ruling out the presence of left atrial thrombus.
    3. Class Ia and Ic antiarrhythmic drugs are suggested for the maintenance of sinus rhythm following cardioversion. In cases where there is impaired left ventricular systolic function, amiodarone might be considered as a treatment option (Strength of recommendation: high, Quality of evidence: low)
- For persistent atrial fibrillation, the decision to use anticoagulation should be based on the CHADS2 score, which is a tool used to assess the risk of stroke occurrence (Strength of recommendation: high, Quality of evidence: low)
- Patients with acute congestive heart failure classified as Killip class ≥III should undergo hemodynamic monitoring using a Swan-Ganz catheter, as recommended (Strength of recommendation: high, Quality of evidence: low)
- Acute congestive heart failure in thyroid storm should be treated according to the Guidelines for the Treatment of Acute Heart Failure (JCS 2011), given the pathophysiology of thyroid storm (Strength of recommendation: high, Quality of evidence: low)

- In cases where the hemodynamic status has not improved with the maximum dose of adrenergic agonists and there is a risk of irreversible multiple organ failure, it is advisable to employ an artificial heart-lung machine as a therapeutic measure (Strength of recommendation: high, Quality of evidence: low)
- Gastrointestinal symptoms like diarrhea, nausea, and vomiting are linked to conditions such as thyrotoxicosis, heart failure, neurological disorders, and gastrointestinal infections. When treating gastrointestinal infections in parallel with thyrotoxicosis, it can help alleviate these symptoms (Strength of recommendation: strong, Quality of evidence: low)
- The administration of high doses of corticosteroids, the presence of coagulopathy related to thyroid storm, and prolonged stays in the intensive care unit with extended mechanical ventilation may increase the risk of gastrointestinal bleeding and mortality. To mitigate these risks, acid-suppressive medications like proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2As) are recommended for patients in these situations (Strength of recommendation: strong, Quality of evidence: low)
- Hepatotoxicity, with or without jaundice, in thyroid storm can result from various factors, including hepatocyte damage due to thyrotoxicosis, heart failure, hepatic-biliary infection, or drug-induced liver injury. Surveys conducted nationwide have shown that a worse prognosis is associated with total bilirubin levels equal to or greater than 3.0 mg/dL. To address hepatic dysfunction, a thorough differential diagnosis of its origin should be performed, and treatment tailored to the underlying cause, including therapeutic plasmapheresis (TPE) for acute hepatic failure, should be considered (Strength of recommendation: strong, Quality of evidence: low)
- Intensive care unit (ICU) admission should be recommended for all thyroid storm patients. Patients with potentially fatal conditions such as shock, DIC, and multiple organ failure should immediately be admitted to the ICU. (Strength of recommendation: strong, Quality of evidence: low)
- The APACHE II score or Sequential Organ Failure Assessment score can be used for the prognostic prediction of thyroid storm. (Strength of recommendation: weak, Quality of evidence: low)
- It is crucial to take preventive measures to avoid thyroid storm in patients with poor adherence who are receiving antithyroid drug (ATD) treatment (Strength of recommendation: high, Quality of evidence: low)
- To prevent the recurrence of thyroid storm in patients who have been effectively managed during the acute phase of thyroid storm, consideration should be given to definitive treatments for Graves' disease, such as

radioiodine treatment or thyroidectomy (Strength of recommendation: high, Quality of evidence: low)

- When patients exhibit elevated body temperature (≥38°C), significant tachycardia (≥130 beats per minute), and symptoms originating from various organ systems such as the central nervous system, cardiovascular system, and gastrointestinal tract, it is crucial to consider the potential occurrence of thyroid storm. When there is suspicion of thyroid storm, healthcare providers should refer to the diagnostic criteria established for thyroid storm [4, 8]. This reference should be made during the initial assessment, which follows the ABCDE (Airway, Breathing, Circulation, Dysfunction of the Central Nervous System, Exposure & Environmental Control) approach to evaluation and treatment. Patients who raise a high suspicion of having thyroid storm based on these criteria should be promptly transferred to a general hospital equipped with an intensive care unit (ICU) and staffed with specialists in endocrinology and other relevant subspecialties (Strength of recommendation: high, Quality of evidence: low).

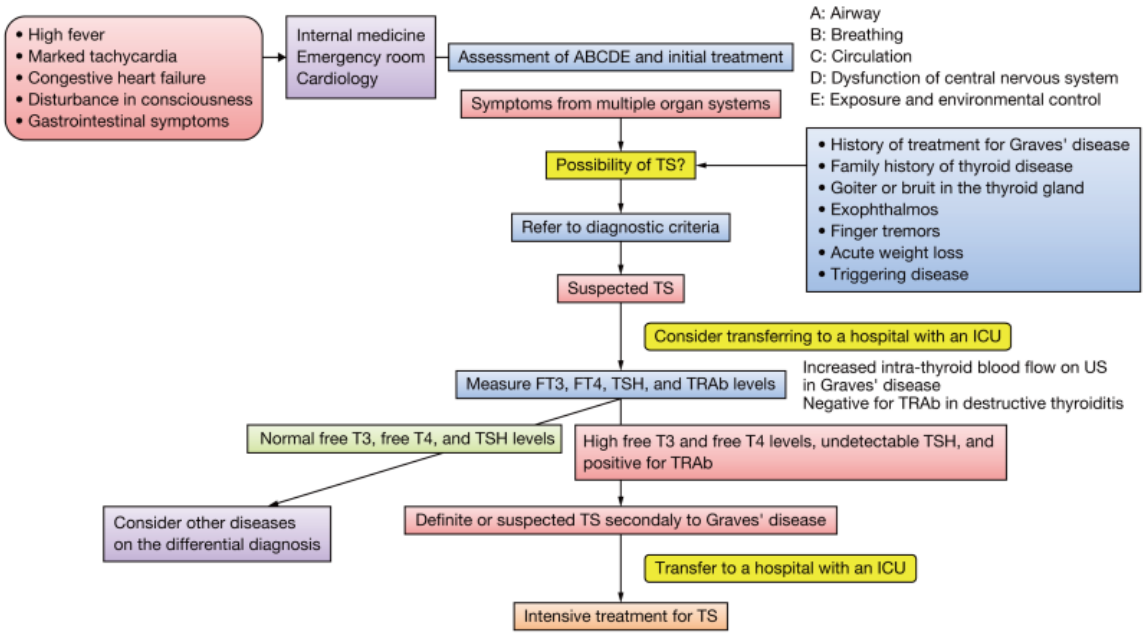

Figure 5. *Algorithm for diagnostic considerations in thyroid storm. Retrieved from the 2016 JTA/JES Guidelines.*

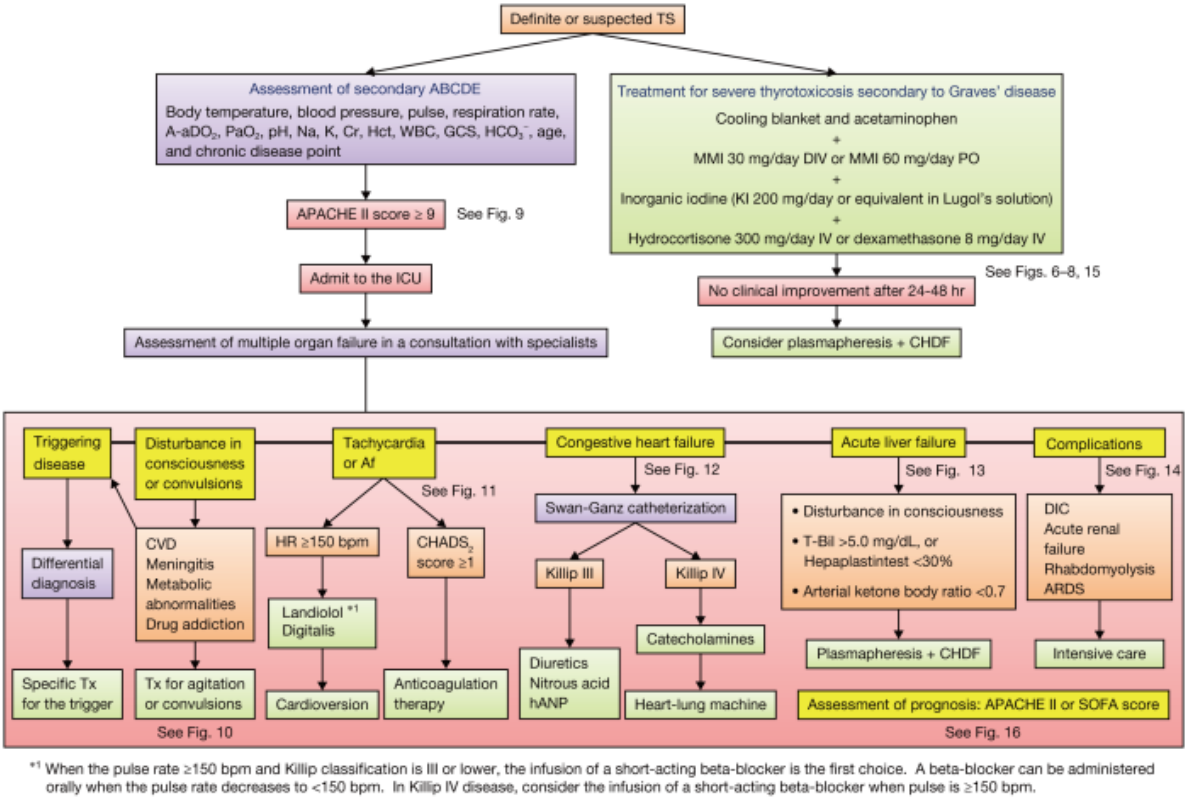

Figure 6. *Treatment algorithm for thyroid storm. Retrieved from the 2016 JTA/JES Guidelines.*

Section 2.0 Drug Therapy in Hyperthyroidism

This section comprises four subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, the third one outlines the drugs that have been withdrawn from the market and the fourth one details other drugs that are not currently SFDA registered.

2.1 Additions

After April 2020, there have been no new drugs for hyperthyroidism that have received SFDA approval.

However, prednisone, prednisolone, rituximab, tocilizumab and azathioprine are used in the treatment of Grave's orbitopathy and are registered on the SFDA. Hence, relevant information pertaining to these drugs can be found below.

2.1.1 Prednisone

This section includes pertinent information regarding the use of Prednisone (Predone®) in Grave's orbitopathy.

Table 17. Prednisone Drug Information

SCIENTIFIC NAME **Prednisone**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	No
PMDA	No
Indication (ICD-10)	E.05
Drug Class	Corticosteroid, Systemic
Drug Sub-class	Glucocorticoid
ATC Code	H02AB07
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use

Dose (Adult) [DDD]*	**Thyroid eye disease, moderate to severe (off-label use): Oral:** 60 to 100 mg once daily for 7 days, then gradually taper dose by 5 to 10 mg/week over 4 to 6 months based on clinical response and then discontinue
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: - **Altered kidney function: Mild to severe impairment:** No dosage adjustment necessary - **Hemodialysis, intermittent (thrice weekly):** No supplemental dose or dosage adjustment necessary - **Peritoneal dialysis:** No dosage adjustment necessary - **CRRT:** No dosage adjustment necessary - **PIRRT (eg, sustained, low-efficiency diafiltration):** No dosage adjustment necessary Hepatic Impairment: There are no dosage adjustments provided in the manufacturer's labeling
Prescribing edits*	ST, CU
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Should be used in conjunction with antithyroid drugs, thyroidectomy, azathioprine, or cyclosporine, in cases where radioactive iodine is used for treatment of orbitopathy.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Considered as second line therapy if the response to primary treatment is inadequate and Grave's orbitopathy remains at a moderate-to-severe and active stage.	

EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Frequency not defined: - Cardiovascular: Bradycardia, cardiomegaly, circulatory shock, edema, heart failure (in susceptible patients), hypertrophic cardiomyopathy (premature infants), myocardial rupture (after recent myocardial infarction), syncope, tachycardia, thrombophlebitis, vasculitis - Dermatologic: Acne vulgaris, allergic dermatitis, atrophic striae, diaphoresis, facial erythema, hyperpigmentation, hypopigmentation, skin atrophy, skin rash, thinning hair (scalp), urticaria - Endocrine & metabolic: Decreased serum potassium, fluid retention, growth retardation (children), hirsutism, hypokalemic alkalosis, menstrual disease, negative nitrogen balance (due to protein catabolism), sodium retention, weight gain - Gastrointestinal: Hiccups, increased appetite, nausea - Genitourinary: Asthenospermia, oligospermia - Hematologic & oncologic: Bruise, petechia - Hepatic: Hepatomegaly, increased serum transaminases - Hypersensitivity: Angioedema - Infection: Sterile abscess

	- Nervous system: Abnormal sensory symptoms, arachnoiditis, headache, increased intracranial pressure (with papilledema), malaise, meningitis, myasthenia, neuritis, neuropathy, paraplegia, paresthesia, seizure, vertigo - Neuromuscular & skeletal: Charcot arthropathy - Respiratory: Pulmonary edema - Miscellaneous: Wound healing impairment <u>Most serious:</u> Adrenal suppression (tertiary adrenal insufficiency), Cardiovascular effects, CNS and psychiatric/behavioral effects, Cushingoid features/Cushing syndrome, GI effects, Hyperglycemia, Infection, Neuromuscular and skeletal effects, and Ocular effects.
Drug Interactions*	<u>Risk X interactions:</u> - Aldesleukin - BCG Products - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Desmopressin - Disulfiram - Indium 111 Capromab Pendetide - Macimorelin - Methotrimeprazine - Mifamurtide - MiFEPRIStone - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Ornidazole - Pimecrolimus

	- Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib - Ruxolitinib (Topical) - Secnidazole - Tacrolimus (Topical) - Talimogene Laherparepvec - Tertomotide - Typhoid Vaccine - Yellow Fever Vaccine
Special Population	- Obesity: Class 1, 2, and 3 obesity (BMI ≥ 30 kg/m2): **Oral:** Non–weight-based dosing: No dosage adjustment necessary. Refer to adult dosing for indication-specific doses. Weight-based dosing: Use ideal body weight to avoid overdosing and subsequent toxicity, especially with longer durations of therapy. Refer to adult dosing for indication-specific doses. - Older adult: Use with caution in older adults with the smallest possible effective dose for the shortest duration. - Pediatric: May affect growth velocity; growth and development should be routinely monitored in pediatric patients.
Pregnancy	Prednisone and its metabolite, prednisolone, cross the placenta. In the mother, prednisone is converted to the active metabolite prednisolone by the liver. Prior to reaching the fetus, prednisolone is converted by placental enzymes back to prednisone. As a result, the level of prednisone remaining in the maternal serum and reaching the fetus are similar; however, the amount

	of prednisolone reaching the fetus is ~8 to 10 times lower than the maternal serum concentration (healthy women at term). Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts; however, information is conflicting and may be influenced by maternal dose, duration/frequency of exposure, and indication for use. Additional data are needed to evaluate potential risks of systemic corticosteroids and other adverse pregnancy outcomes (eg, gestational diabetes mellitus, low birth weight, preeclampsia, preterm birth). Hypoadrenalism may occur in newborns following maternal use of corticosteroids in pregnancy; monitor infants exposed to prolonged or high doses of prednisone in utero. Due to pregnancy-induced physiologic changes, clearance of prednisone may be increased (may be dose dependent). Prednisone is a preferred oral corticosteroid for the treatment of maternal conditions during pregnancy because placental enzymes limit passage to the embryo. Prednisone ≤10 mg/day is acceptable for use in pregnant patients with rheumatic and musculoskeletal diseases. Higher doses should be tapered to <20 mg/day with the addition of pregnancy compatible immunosuppressants. Stress dosing is not recommended during vaginal delivery. Corticosteroids may be used as needed for disease flares in pregnant patients

	with inflammatory bowel disease; however, maintenance therapy should be avoided. Uncontrolled asthma is associated with adverse events in pregnancy (increased risk of perinatal mortality, preeclampsia, preterm birth, low birth weight infants, cesarean delivery, and the development of gestational diabetes). Poorly controlled asthma or asthma exacerbations may have a greater fetal/maternal risk than what is associated with appropriately used asthma medications. Maternal treatment improves pregnancy outcomes by reducing the risk of some adverse events. Inhaled corticosteroids are recommended for the treatment of asthma during pregnancy; however, systemic corticosteroids, including prednisone, should be used to control acute exacerbations or treat severe persistent asthma. Maternal asthma symptoms should be monitored monthly during pregnancy. Prednisone is recommended for use in fetal-neonatal alloimmune thrombocytopenia and pregnancy-associated immune thrombocytopenia. Prednisone is the preferred immunosuppressant for the treatment of myasthenia gravis in pregnancy.
Lactation	Prednisone and its metabolite, prednisolone, are present in breast milk. According to the manufacturer, prednisolone breast milk concentrations are 5% to 25% of the maternal serum levels, providing a total infant dose <1% of the maternal dose. Actual concentrations are dependent upon maternal dose. Peak

	concentrations of prednisone and prednisolone in breast milk occur ~2 to 3 hours after an oral maternal dose; the half-life in breast milk is 1.9 hours (prednisone) and 4.2 hours (prednisolone). In a study which included six mother-infant pairs, adverse events were not observed in breastfeeding infants (maternal prednisone dose not provided). The manufacturer notes that maternal use of high doses of systemic corticosteroids have the potential to cause adverse events in a breastfeeding infant (eg, growth suppression, interfere with endogenous corticosteroid production); therefore, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. The lowest effective dose should be used to minimize potential infant exposure via breast milk. Corticosteroids are generally considered acceptable in breastfeeding women when used in usual doses; however, monitoring of the breastfeeding infant is recommended (WHO 2002). Prednisone is one of the oral corticosteroids preferred for use in breastfeeding women. Breastfeeding is acceptable for patients with rheumatic and musculoskeletal diseases taking prednisone <20 mg/day. If there is concern about exposure to the infant, some guidelines recommend waiting up to 4 hours after the maternal dose of an oral systemic corticosteroid before breastfeeding in order to

	decrease potential exposure to the breastfeeding infant (based on a study using prednisolone)
Contraindications	Hypersensitivity to prednisone or any component of the formulation; administration of live or live attenuated vaccines with immunosuppressive doses of prednisone; systemic fungal infections. *Canadian labeling:* Additional contraindications (not in US labeling): Herpes simplex of the eye, measles, or chickenpox (except when being used for short-term or emergency therapy); peptic ulcer; nonspecific ulcerative colitis; diverticulitis; viral or bacterial infection not controlled by anti-infectives.
Monitoring Requirements	Blood pressure; weight; serum glucose; electrolytes; creatine kinase; growth in pediatric patients; presence of infection, bone mineral density; assess HPA axis suppression (eg, ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test); Hgb, occult blood loss; chest x-ray (at regular intervals during prolonged therapy); IOP with therapy >6 weeks, eye examination (periodically during therapy
Precautions	- Adrenal suppression: May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children. - Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative

	colitis [nonspecific]) due to perforation risk. - Head injury: Increased mortality was observed in patients receiving high-dose IV methylprednisolone; high-dose corticosteroids should not be used for the management of head injury. - Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; effects may be enhanced. - Myasthenia gravis: Use may cause transient worsening of myasthenia gravis (MG) (eg, within first 2 weeks of treatment); monitor for worsening MG. - Ocular disease: Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex. - Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur. - Seizure disorders: Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. - Systemic sclerosis: Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with corticosteroid use. Monitor BP and renal function in patients

	with systemic sclerosis treated with corticosteroids. - Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *prednisone* for the treatment of grave's orbitopathy**. Despite this, ***prednisone*** has been available on the market for many years.

CONCLUSION STATEMENT – PREDNISONE

Prednisone is mentioned in the guidelines as an alternative treatment for moderate-to-severe grave's orbitopathy since IV glucocorticoids are usually preferred. Furthermore, a prospective, single-blind, randomized study was conducted to compare the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy. This study concluded that High-dose intravenous glucocorticoids and oral glucocorticoids (when combined with orbital radiotherapy) have proven to be effective treatments for severe Graves' ophthalmopathy. However, it appears that the intravenous administration method is more efficient, better tolerated, and associated with a reduced incidence of side effects compared to the oral approach[12]. Therefore, it is recommended to add prednisone to the SFDA drug list for this indication.

2.1.2 Prednisolone

This section includes pertinent information regarding the use of Prednisone (GUPISONE®) in Grave's orbitopathy.

Table 18. Prednisolone Drug Information

SCIENTIFIC NAME **Prednisolone**	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	E.05
Drug Class	Corticosteroid, Systemic
Drug Sub-class	Glucocorticoid
ATC Code	H02AB06
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	**Thyroid eye disease, moderate to severe (off-label use): Oral:** 60 to 100 mg once daily for 7 days, then gradually taper dose by 5 to 10 mg/week over 4 to 6 months based on clinical response and then discontinue
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: - **Altered kidney function: Mild to severe impairment:** No dosage adjustment necessary - **Hemodialysis, intermittent (thrice weekly):** No

	supplemental dose or dosage adjustment necessary - **Peritoneal dialysis:** No dosage adjustment necessary - **CRRT:** No dosage adjustment necessary - **PIRRT (eg, sustained, low-efficiency diafiltration):** No dosage adjustment necessary <u>Hepatic Impairment:</u> There are no dosage adjustments provided in the manufacturer's labeling
Prescribing edits*	ST, CU
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Should be used in conjunction with antithyroid drugs, thyroidectomy, azathioprine, or cyclosporine, in cases where radioactive iodine is used for treatment of orbitopathy.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Considered as second line therapy if the response to primary treatment is inadequate and Grave's orbitopathy remains at a moderate-to-severe and active stage.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	<u>Frequency not defined:</u> - Cardiovascular: Bradycardia, cardiomegaly, cholesterol embolus syndrome, circulatory shock, edema, heart failure, hypertrophic cardiomyopathy (premature infants), myocardial rupture (after recent myocardial infarction), syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis

	- Dermatologic: Acne vulgaris, allergic dermatitis, atrophic striae, diaphoresis, dry scalp, ecchymoses, facial erythema, hyperpigmentation, hypopigmentation, inadvertent suppression of skin test reaction, skin atrophy, skin rash, thinning hair (scalp), urticaria - Endocrine & metabolic: Decreased serum potassium, fluid retention, growth retardation (children), hirsutism, HPA-axis suppression, hypokalemic alkalosis, impaired glucose tolerance, menstrual disease, negative nitrogen balance (due to protein catabolism), sodium retention, weight gain - Gastrointestinal: Hiccups, impaired intestinal carbohydrate absorption, increased appetite, nausea, pancreatitis - Genitourinary: Asthenospermia, oligospermia - Hematologic & oncologic: Petechia - Hepatic: Hepatomegaly, increased liver enzymes - Hypersensitivity: Nonimmune anaphylaxis - Infection: Sterile abscess - Nervous system: Abnormal sensory symptoms, amyotrophy, arachnoiditis, headache, increased intracranial pressure (with papilledema), insomnia, malaise, meningitis, myasthenia, neuritis, neuropathy, paraplegia,

	paresis (paraparesis), paresthesia, seizure, vertigo - Neuromuscular & skeletal: Aseptic necrosis of femoral head, aseptic necrosis of humeral head, Charcot arthropathy, rupture of tendon - Ophthalmic: Exophthalmos - Respiratory: Pulmonary edema - Miscellaneous: Wound healing impairment <u>Most serious:</u> Bradycardia, cardiomegaly, cholesterol embolus syndrome, circulatory shock, edema, heart failure, hypertrophic cardiomyopathy (premature infants), myocardial rupture (after recent myocardial infarction), syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis, paresthesia, seizure, septic necrosis of femoral head, aseptic necrosis of humeral head septic necrosis of femoral head, aseptic necrosis of humeral head, pulmonary edema
Drug Interactions*	<u>Risk X interactions:</u> - Aldesleukin - BCG Products - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Desmopressin - Indium 111 Capromab Pendetide - Macimorelin - Mifamurtide - MiFEPRIStone - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec

	- Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib - Ruxolitinib (Topical) - Secnidazole - Tacrolimus (Topical) - Talimogene Laherparepvec - Tertomotide - Typhoid Vaccine - Yellow Fever Vaccine
Special Population	- Older adult: Use with caution in older adults with the smallest possible effective dose for the shortest duration. - Pediatric: May affect growth velocity; growth should be routinely monitored in pediatric patients.
Pregnancy	Prednisolone crosses the placenta; prior to reaching the fetus, prednisolone is converted by placental enzymes to prednisone. As a result, the amount of prednisolone reaching the fetus is ~8 to 10 times lower than the maternal serum concentration (healthy individuals at term; similar results observed with preterm pregnancies complicated by HELLP syndrome). Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts or decreased birth weight; however, information is conflicting and may be influenced by maternal dose/indication for use. Hypoadrenalism may occur in newborns following maternal use of corticosteroids in pregnancy; monitor.

	Prednisolone is a preferred oral corticosteroid for the treatment of maternal conditions during pregnancy because placental enzymes limit passage to the embryo. When systemic corticosteroids are needed in pregnancy for rheumatic disorders, nonfluorinated corticosteroids such as prednisolone are preferred. Chronic high doses should be avoided. Prednisolone may be used (alternative agent) to treat primary adrenal insufficiency (PAI) in pregnancy. Pregnant patients with PAI should be monitored at least once each trimester. Prednisolone may be used to treat patients during pregnancy who require therapy for congenital adrenal hyperplasia. For dermatologic disorders in pregnant patients, systemic corticosteroids are generally not preferred for initial therapy; should be avoided during the first trimester; and used during the second or third trimester at the lowest effective dose. Topical agents are preferred for managing atopic dermatitis in pregnancy; for severe symptomatic or recalcitrant atopic dermatitis, a short course of prednisolone may be used during the third trimester. Uncontrolled asthma is associated with adverse events in pregnancy (increased risk of perinatal mortality, preeclampsia, preterm birth, low birth weight infants, cesarean delivery, and the development of gestational diabetes). Poorly controlled asthma or asthma exacerbations may have a greater

	fetal/maternal risk than what is associated with appropriately used asthma medications. Maternal treatment improves pregnancy outcomes by reducing the risk of some adverse events (eg, preterm birth, gestational diabetes). Inhaled corticosteroids are recommended for the treatment of asthma during pregnancy; however, systemic corticosteroids should be used to control acute exacerbations or treat severe persistent asthma. Maternal asthma symptoms should be monitored monthly during pregnancy. Prednisolone is an alternative corticosteroid for use in pregnant patients with severe or critical COVID-19 due to limited placental transfer. Treatment algorithms are available for pregnant patients with severe or critical COVID-19 who require corticosteroids. In general, the treatment of COVID-19 during pregnancy is the same as in nonpregnant patients. However, because data for most therapeutic agents in pregnant patients are limited, treatment options should be evaluated as part of a shared decision-making process. The risk of severe illness from COVID-19 infection is increased in symptomatic pregnant patients compared to nonpregnant patients. Information related to the treatment of COVID-19 during pregnancy continues to emerge; refer to current guidelines for the treatment of pregnant patients.
Lactation	Prednisolone is present in breast milk. Information related to the presence of prednisolone in breast milk is available from a study of 6 lactating women on

	maintenance treatment with prednisolone 10 to 80 mg/day. The highest breast milk concentration (317 ng/mL) was observed 1 hour following an 80 mg dose in a patient 53 days postpartum; breast milk concentrations decreased to <100 ng/mL 4 hours after the maternal dose. Using data from all women in this study, milk concentrations were 5% to 25% of the maternal serum concentration with peak concentrations occurring ~1 hour after the maternal dose. The milk/plasma ratio was found to be 0.2 with doses ≥30 mg/day and 0.1 with doses <30 mg/day . Using a milk concentration of 317 ng/mL, the estimated exposure to the breastfeeding infant would be 0.05 mg/kg/day (relative infant dose 4% based on a weight-adjusted maternal dose of 80 mg/day). In general, breastfeeding is considered acceptable when the relative infant dose of a medication is <10%. One manufacturer notes that when used systemically, maternal use of corticosteroids have the potential to cause adverse events in a breastfeeding infant (eg, growth suppression, interfere with endogenous corticosteroid production). Therefore, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Corticosteroids are generally considered acceptable in patients who are breastfeeding when used in usual doses; however, monitoring of the

	breastfeeding infant is recommended (WHO 2002). Prednisolone is classified as a nonfluorinated corticosteroid; when systemic corticosteroids are needed in a lactating patient for rheumatic disorders, low doses of nonfluorinated corticosteroids are preferred. If there is concern about exposure to the infant, some guidelines recommend waiting 4 hours after the maternal dose of an oral systemic corticosteroid before breastfeeding in order to decrease potential exposure to the breastfed infant
Contraindications	Hypersensitivity to prednisolone or any component of the formulation; administration of live or live attenuated virus vaccines (with immunosuppressive doses of corticosteroids); systemic fungal infections. Canadian labeling: Additional contraindications (not in US labeling): Hepatitis; herpes; shingles; varicella; measles; uncontrolled active infections; uncontrolled psychotic states.
Monitoring Requirements	BP; weight; serum glucose; electrolytes; growth in pediatric patients; presence of infection, bone mineral density; assess HPA axis suppression (eg, ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test); Hgb, occult blood loss; chest x-ray (at regular intervals during prolonged therapy); IOP with therapy >6 weeks, eye examination (periodically during therapy)
Precautions	- Adrenal suppression: May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger

	children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Adult patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections. - Anaphylactoid reactions: Rare cases of anaphylactoid reactions have been observed in patients receiving corticosteroids. - Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, cause activation of latent infections, mask acute infection (including fungal infections) or prolong or exacerbate viral infections or limit response to killed or inactivated vaccines. Exposure to chickenpox or measles should be avoided;

	corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria or viral hepatitis. Close observation is required in patients with tuberculosis (TB) infection (latent TB) and/or TB reactivity; restrict use in TB disease (active TB) (only fulminating or disseminated TB in conjunction with antituberculosis treatment). Amebiasis should be ruled out in any patient with recent travel to tropic climates or unexplained diarrhea prior to initiation of corticosteroids. Use with extreme caution in patients with *Strongyloides* infections; hyperinfection, dissemination and fatalities have occurred. - Kaposi sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered. - Myopathy: Acute myopathy has been reported with high dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed. - Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including severe depression,

	euphoria, insomnia, mood swings, personality changes, and frank psychotic manifestations. Preexisting psychiatric conditions may be exacerbated by corticosteroid use. - Cardiovascular disease: Use with caution in patients with HF and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension. Use with caution following acute MI; corticosteroids have been associated with myocardial rupture. - Diabetes: Use corticosteroids with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia. - Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess or other pyogenic infection) due to perforation risk. Avoid ethanol may enhance gastric mucosal irritation. - Head injury: Increased mortality was observed in patients receiving high-dose IV methylprednisolone. High-dose corticosteroids should not be used for the management of head injury. - Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis;

	long-term use has been associated with fluid retention. - Kidney impairment: Use with caution in patients with kidney impairment; fluid retention may occur. - Myasthenia gravis: Use may cause transient worsening of myasthenia gravis (MG) (eg, within first 2 weeks of treatment); monitor for worsening MG. - Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex. Not recommended for the treatment of optic neuritis; may increase frequency of new episodes. Consider routine eye exams in chronic users. - Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures. - Seizure disorders: Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. - Systemic sclerosis: Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis

	incidence has been observed with corticosteroid use. Monitor BP and kidney function in patients with systemic sclerosis treated with corticosteroids. - Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *prednisone* for the treatment of grave's orbitopathy**. Despite this, ***prednisolone*** has been available on the market for many years.

CONCLUSION STATEMENT – PREDNISOLONE

Prednisone is mentioned in the guidelines as an alternative treatment for moderate-to-severe grave's orbitopathy since IV glucocorticoids are usually preferred. Furthermore, a prospective, single-blind, randomized study was conducted to compare the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy. This study concluded that High-dose intravenous glucocorticoids and oral glucocorticoids (when combined with orbital radiotherapy) have proven to be effective treatments for severe Graves' ophthalmopathy. However, it appears that the intravenous administration method is more efficient, better tolerated, and associated with a reduced incidence of side effects compared to the oral approach.[13] Therefore, it is recommended to add prednisone to the SFDA drug list for this indication.

2.1.3 Tocilizumab

This section includes pertinent information regarding the use of Prednisone (ACTEMRA®) in Grave's orbitopathy.

Table 19. Tocilizumab Drug Information

SCIENTIFIC NAME **Tocilizumab**	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	E.05
Drug Class	Antirheumatic, Disease Modifying, Monoclonal Antibody
Drug Sub-class	Interleukin-6 Receptor Antagonist
ATC Code	L04AC07
Pharmacological Class (ASHP)	92:36 - Disease-modifying Antirheumatic Agents
DRUG INFORMATION	
Dosage Form	Concentrate for solution for infusion
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy:** 8 mg/kg IV at weeks 0, 4, 8, and 12[13]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: CrCl ≥30 mL/minute: No dosage adjustment necessary. CrCl <30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, based on tocilizumab's molecular weight (148

	kDa), it is unlikely to be significantly renally eliminated Hepatic Impairment: Hepatic impairment prior to treatment initiation: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	ST, PA
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): Should be prior authorized for patients who have tried first-line of therapy and failed.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Considered as second-line therapy if the response to primary treatment is inadequate and Graves' orbitopathy remains at a moderate-to-severe and active stage.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Increased serum cholesterol , constipation, neutropenia, increased serum alanine aminotransferase, increased serum aspartate aminotransferase, infusion-related reaction Most serious: Deep vein thrombosis, hypertension, peripheral edema, septic shock, hyperglycemia, hypoglycemia, leukopenia, thrombocytopenia, antibody development, acute kidney injury
Drug Interactions*	Risk X interactions: - Abrocitinib - Anifrolumab

	- Anti-TNF Agents - Baricitinib - BCG Products - Biologic Disease-Modifying Antirheumatic Drugs (DMARDs) - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Filgotinib - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib - Ruxolitinib (Topical) - Tacrolimus (Topical) - Tertomotide - Tofacitinib - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - Yellow Fever Vaccine
Special Population	N/A
Pregnancy	Tocilizumab crosses the placenta. Tocilizumab is a humanized monoclonal antibody (IgG_1). Human IgG crosses the placenta. Fetal exposure is dependent upon the IgG subclass, maternal serum concentrations, placental integrity, newborn birth weight, and gestational age, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis and the highest during the third trimester.

	Tocilizumab was not detected in umbilical cord blood, infant serum, or maternal serum at delivery in a patient who received her last dose 23 weeks prior to delivery. Postmarketing data reviewed through 2014 have not shown an increased rate of congenital malformations or a pattern of specific malformations following in utero exposure to tocilizumab. The review included pregnancy outcome data from 288 women who received tocilizumab for rheumatic disorders; the majority received a dose during the first trimester or within 6 weeks of conception. Using these data, the incidence of preterm birth and spontaneous abortion may be increased when compared to the background rate, but these outcomes may also be influenced by maternal disease and concomitant medications. Additional outcome data are limited. Until additional data are available, tocilizumab is not currently recommended for the treatment of rheumatic and musculoskeletal diseases during pregnancy. Tocilizumab should be discontinued once pregnancy is confirmed Data collection to monitor pregnancy and infant outcomes following exposure to tocilizumab is ongoing.
Lactation	Tocilizumab is present in colostrum and breast milk. In a report of 2 cases, breast milk concentrations peaked ~3 days after an IV maternal dose, then gradually decreased. In a third case, tocilizumab was detected in the serum of 1 infant at birth following in utero exposure;

	however, concentrations rapidly decreased and were not detectable by 4 weeks of age, even though the infant was exclusively breastfed. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Although data related to use in lactating patients are limited, adverse events have not been reported in breastfed infants. Concentrations of tocilizumab are expected to be limited in breast milk due to large molecular weight. Also, because tocilizumab is unlikely to be absorbed via the infant GI tract, use of tocilizumab may be considered in patients who are breastfeeding.
Contraindications	Hypersensitivity to prednisolone or any component of the formulation; administration of live or live attenuated virus vaccines (with immunosuppressive doses of corticosteroids); systemic fungal infections. Canadian labeling: Additional contraindications (not in US labeling): Hepatitis; herpes; shingles; varicella; measles; uncontrolled active infections; uncontrolled psychotic states.
Monitoring Requirements	Chronic therapy: Latent TB screening prior to therapy initiation (all patients); neutrophils, platelets (prior to therapy, 4 to 8 weeks after start of therapy, and every 3 months thereafter [rheumatoid arthritis {RA}, giant cell arteritis {GCA}, systemic sclerosis (scleroderma)-associated interstitial lung disease {SSC-ILD}]); ALT/AST, alkaline phosphatase,

	and total bilirubin (prior to therapy, every 4 to 8 weeks after start of therapy for the first 6 months, and every 3 months thereafter [RA, GCA, SSc-ILD]); neutrophils, platelets, ALT/AST (prior to therapy, at second administration, and every 2 to 4 weeks [systemic juvenile idiopathic arthritis] or 4 to 8 weeks [polyarticular juvenile idiopathic arthritis] thereafter); additional liver function tests (eg, bilirubin) as clinically indicated; lipid panel (prior to and 4 to 8 weeks following initiation of therapy, then subsequently according to current guidelines); monitor all patients for signs and symptoms of infection (prior to, during, and after therapy); signs and symptoms of CNS demyelinating disorders; new onset abdominal symptoms.
Precautions	- Herpes zoster reactivation: Herpes zoster reactivation has been reported. - Hyperlipidemia: Therapy is associated with increases in total cholesterol, triglycerides, low-density lipoprotein, and/or high-density lipoprotein. - Malignancy: Use of tocilizumab may affect defenses against malignancies; impact on the development and course of malignancies is not fully defined; however, malignancies were observed in clinical trials. - Demyelinating CNS disease: Use with caution in patients with preexisting or recent onset CNS demyelinating disorders; rare cases of CNS demyelinating disorders (multiple sclerosis and

	chronic inflammatory demyelinating polyneuropathy) have occurred. - Hepatic impairment: Use with caution in hepatic impairment; see "Dosage: Hepatic Function Impairment" for additional information. - Tuberculosis: Consider anti-tuberculosis (TB) treatment in patients with a history of latent or active TB infection or disease (latent or active TB) if adequate treatment course cannot be confirmed, and for patients with risk factors for TB despite a negative test.
Black Box Warning	Risk of serious infections
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *tocilizumab* for the treatment of grave's orbitopathy**. Despite this, ***tocilizumab*** has been available on the market for many years.

CONCLUSION STATEMENT – TOCILIZUMAB

Tocilizumab can be used as second-line therapy if the response to primary treatment is inadequate and Graves' orbitopathy remains at a moderate-to-severe and active stage as mentioned in the guidelines. In a randomized trial, 32 patients with thyroid eye disease were randomly assigned to tocilizumab (8 mg/kg) or placebo IV at 0, 4, 8, and 12 weeks. Treatment with tocilizumab was associated with greater improvement in clinical activity score at 16 weeks (93.3 versus 58.8% with placebo) and improvement in a composite ophthalmic score at 16 weeks (73.3 versus 29.4%), but no significant differences between groups at 40 weeks[13]. Therefore, it is recommended to include Tocilizumab in the SFDA drug list for this indication.

2.1.4 Rituximab

This section includes pertinent information regarding the use of Prednisone (MABTHERA®), (TRUXIMA®), (Rixathon®), (Ruxience®) in Grave's orbitopathy.

Table 20. Rituximab Drug Information

SCIENTIFIC NAME **Rituximab**	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	E.05
Drug Class	Monoclonal Antibody; Antirheumatic, Miscellaneous; Immunosuppressant Agent
Drug Sub-class	Anti-CD20
ATC Code	L01XC02
Pharmacological Class (ASHP)	10:00 - Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Concentrate for solution for infusion
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Active, moderate-to-severe thyroid eye disease: IV:** - single dose of 100 mg[14] - single dose of 2000 mg[15] - single dose of 500 mg[15]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: **Altered kidney function: IV:** No dosage adjustment necessary for any degree of kidney dysfunction **Augmented renal clearance (measured urinary CrCl ≥130**

	mL/minute/1.73 m2): Augmented renal clearance (ARC) is a condition that occurs in certain critically ill patients without organ dysfunction and with normal serum creatinine concentrations. Younger patients (<55 years of age) admitted post trauma or major surgery are at highest risk for ARC, as well as those with sepsis, burns, or hematologic malignancies. An 8- to 24-hour measured urinary CrCl is necessary to identify these patients IV: No dosage adjustment necessary **Hemodialysis, intermittent (thrice weekly)**: Not significantly dialyzed IV: No dosage adjustment or supplemental dose necessary. **Peritoneal dialysis:** In general, unlikely to be significantly dialyzed (expert opinion); however, significant amounts reported to be dialyzed in a patient with nephrotic syndrome. IV: No dosage adjustment necessary **CRRT:** IV: No dosage adjustment necessary. **PIRRT** (eg, sustained, low-efficiency diafiltration): IV: No dosage adjustment necessary <u>Hepatic Impairment:</u> There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	ST, PA, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialty physician.	
PA (Prior Authorization): Should be prior authorized for patients who have tried first-line of therapy and failed.	
QL (Quantity Limit): N/A	

ST (Step Therapy): Considered as second-line therapy if the response to primary treatment is inadequate and Graves' orbitopathy remains at a moderate-to-severe and active stage.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- <u>Most common:</u> Cardiac disorder, flushing, hypertension, peripheral edema, night sweats, pruritus, skin rash, hypophosphatemia, weight gain, abdominal pain, diarrhea, nausea, anemia, febrile neutropenia , hypogammaglobulinemia, leukopenia, lymphocytopenia ,neutropenia, thrombocytopenia, hepatobiliary disease, increased serum alanine aminotransferase, angioedema, antibody development, bacterial infection, herpes simplex infection, parvovirus B19 seroconversion, varicella zoster infection, hepatitis C, and lower respiratory tract infection), serious infection, chills, fatigue, headache, insomnia, pain, peripheral sensory neuropathy, arthralgia, asthenia, muscle spasm, bronchitis, cough, epistaxis, nasopharyngitis, pulmonary disease, pulmonary toxicity, rhinitis, upper respiratory tract infection, fever, infusion related reaction <u>Most serious:</u> Hepatitis B virus reactivation, hypogammaglobulinemia and infection, infusion-related reactions, progressive multifocal leukoencephalopathy (PML)
Drug Interactions*	<u>Risk X interactions:</u>

	- Abrocitinib - Anifrolumab - Baricitinib - BCG (Intravesical) - BCG Products - Belimumab - Biologic Disease-Modifying Antirheumatic Drugs (DMARDs) - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Dipyrone - Fexinidazole - Filgotinib - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib - Ruxolitinib (Topical) - Tacrolimus (Topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - Yellow Fever Vaccine
Special Population	• Granulomatosis with polyangiitis/microscopic polyangiitis: The safety of concomitant immunosuppressants other than corticosteroids has not been evaluated in patients with

	granulomatosis with polyangiitis or microscopic polyangiitis after rituximab-induced B-cell depletion. • Older adult: There is a higher risk of cardiac (supraventricular arrhythmia) and pulmonary adverse events (pneumonia, pneumonitis), and the incidence of grade 3 or 4 adverse reactions are higher in patients ≥65 years of age. • Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold biologic disease-modifying antirheumatic drugs (DMARDs) prior to surgery and plan surgery after the next dose is due. Surgery can occur after holding medication for 1 full dosing cycle (eg, for medications administered every 4 weeks, schedule surgery 5 weeks from last administered dose); therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk). Decisions to withhold therapy should be based on shared decision making; ensure the patient and their provider weigh risks of interrupting therapy and disease control versus risks of continuing therapy and surgical complications.

	• Pemphigus vulgaris: The safety of concomitant immunosuppressants other than corticosteroids has not been evaluated in patients with pemphigus vulgaris after rituximab-induced B-cell depletion. • Rheumatoid arthritis: There are limited data on the safety of other biologics or DMARDs other than methotrexate in patients with rheumatoid arthritis (RA) with B-cell depletion following rituximab treatment. Monitor patients closely for infection if biologic agents or DMARDs are used concomitantly. The use of rituximab is not recommended in RA patients who have not had prior inadequate response to one or more tumor necrosis factor antagonists.
Pregnancy	Rituximab crosses the placenta and can be detected in the newborn. Rituximab is a humanized monoclonal antibody (IgG1). Human IgG crosses the placenta. Fetal exposure is dependent upon the IgG subclass, maternal serum concentrations, placental integrity, newborn birth weight, and GA, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis and the highest during the third trimester. In one infant born at 41 weeks' gestation, in utero exposure occurred from week 16 to 37; rituximab concentrations were higher in the neonate at birth (32,095 ng/mL) than the mother (9,750 ng/mL) and still

	measurable at 18 weeks of age (700 ng/mL infant; 500 ng/mL mother). Outcome data following maternal use of rituximab during pregnancy are available. Although reassuring, available safety data are limited. B-cell lymphocytopenia generally lasting <6 months may occur following in utero exposure. Infants and newborns exposed to rituximab during pregnancy should be monitored for infection. The European Society for Medical Oncology has published guidelines for diagnosis, treatment, and follow-up of cancer during pregnancy. The guidelines recommend referral to a facility with expertise in cancer during pregnancy and encourage a multidisciplinary team (obstetrician, neonatologist, oncology team) approach. Based on limited data, if pregnancy occurs during rituximab treatment, rituximab should ideally be withheld. However, if postponing rituximab would significantly compromise maternal outcomes in patients diagnosed with B-cell lymphoma during pregnancy, rituximab use is not discouraged. An international consensus panel has published guidelines for hematologic malignancies during pregnancy. In patients with aggressive lymphomas, rituximab (as a component of the R-CHOP chemotherapy regimen) may be administered in the second and third trimesters, however, it should be avoided within 3 weeks of anticipated delivery. Although approved for the treatment of rheumatoid arthritis, based on available

	data, rituximab should be discontinued once pregnancy is detected in patients treated for rheumatic and musculoskeletal diseases; treatment during pregnancy should only be considered for pregnant patients with life- or organ-threatening disease. Rituximab is used off-label for the treatment of primary immune thrombocytopenia (ITP). Although data specific to pregnancy are limited, use can be considered in pregnant patients with very severe ITP. Monitor for perinatal and neonatal immunosuppression and subsequent infection. Rituximab has been evaluated off-label for neurological indications such as multiple sclerosis and neuromyelitis optica spectrum disorder (NMOSD). Maternal NMOSD may be associated with adverse pregnancy outcomes, including miscarriage and preeclampsia. Data related to the treatment of NMOSD during pregnancy are limited; however, use of rituximab prior to pregnancy may prevent pregnancy-related attacks
Lactation	Rituximab is present in breast milk. Data related to the presence of rituximab in breast milk are available from case reports and small studies: - The presence of rituximab in breast milk was evaluated following administration of rituximab 1,000 mg for the treatment of granulomatosis with polyangiitis to a woman within 6 months' postpartum. Following infusion, breast milk and maternal serum concentrations

	were evaluated for 4 days, beginning 7 days after administration. Breast milk concentrations of rituximab (0.4 to 0.6 mcg/mL) were significantly less than those in the maternal serum (110 to 130 mcg/mL). Corresponding serum concentrations were not available from the fully breastfed infant; however, serious infections were not observed and normal growth and development were noted. - Breast milk was sampled for 4 consecutive days in a patient treated with a dose of rituximab 500 mg at 4 months' postpartum. The maximum rituximab concentration in breast milk was 0.004 mcg/mL, 2 days after the maternal dose. Rituximab was not detected in the infant serum when tested 4 and 24 hours after the dose. The authors of this study calculated the relative infant dose (RID) of rituximab to be 0.006% to 0.007% of the weight-adjusted maternal dose. - Data are available from a prospective study of 9 lactating women with multiple sclerosis treated with rituximab. Breast milk samples were obtained prior to the infusion and at intervals up to 30 days following a 500 mg or 1,000 mg dose (30 samples obtained). The median maximum milk concentration of rituximab was 0.074 mcg/mL (range: 0.061 to 0.12 mcg/mL). Using the maximum milk concentrations

	from 4 women who provided serial samples, the authors of this study calculated the RID of rituximab to be 0.1% of the weight-adjusted maternal dose, providing an estimated daily infant dose via breast milk of 0.011 mg/kg/day. There were no serious infections reported in the 5 infants who were breastfed. In addition, they were reported to have normal growth and development up to 12 months of age. - Rituximab concentrations were evaluated in 6 mother-infant pairs following maternal treatment for relapsing-remitting multiple sclerosis. Rituximab infusions (500 mg n = 5; 1,000 mg n = 1) were initiated between 13 and 31 days' postpartum. Breast milk was sampled prior to dosing, then 2, 7, ~22, ~66, and ~110 days after the infusion (the later samples were obtained after 1, 3, and 5 half-lives). Maximum concentrations of rituximab in breast milk occurred ~4.5 days after the infusion. The highest breast milk concentrations were 0.09 to 0.25 mcg/mL. Using the maximum breast milk concentration (0.25 mcg/mL), which occurred following a dose of rituximab 1,000 mg, authors of the study calculated the RID to be 0.26% of the weight-adjusted maternal dose, providing an estimated daily infant dose via breast milk of 0.038 mg/kg/day.

	Serum concentrations of rituximab in all breastfed infants were <0.01 mcg/mL, and all but 2 cases were below the lower limit of quantification (0.005 mcg/mL). Infant B-cell counts were in the normal range. - In general, breastfeeding is considered acceptable when the RID of a medication is <10%. - According to the manufacturer, breastfeeding is not recommended during treatment and for 6 months after the last dose of rituximab. However, based on available data, rituximab is considered compatible with breastfeeding in patients treated for rheumatic and musculoskeletal diseases. In addition, rituximab is unlikely to be absorbed by the infant gastrointestinal tract following exposure via breast milk.
Contraindications	There are no contraindications listed in the manufacturer's US labeling. Canadian labeling: Known type 1 hypersensitivity or anaphylactic reaction to murine proteins, Chinese Hamster Ovary (CHO) cell proteins, or any component of the formulation; patients who have or have had progressive multifocal leukoencephalopathy (PML); patients with severe, active infections.
Monitoring Requirements	- CBC with differential and platelets (obtain prior to treatment and prior to each treatment course, and at weekly to monthly intervals and more frequently in patients with lymphoid malignancies, or at 2-

	to 4-month intervals in rheumatoid arthritis patients, granulomatosis with polyangiitis and microscopic polyangiitis); continue to monitor for cytopenias after the final rituximab dose and until resolution. Monitor electrolytes (in patients at risk for tumor lysis syndrome [TLS]), renal function (in patients at risk for TLS or nephrotoxicity), fluid/hydration status balance. Monitor BP and vital signs. Evaluate pregnancy status (prior to treatment initiation in patients who may become pregnant). - Hepatitis B virus reactivation screening: Screen all patients for hepatitis B virus (HBV) infection prior to therapy initiation (eg, hepatitis B surface antigen [HBsAG] and hepatitis B core antibody measurements). Screen patients for latent infections (eg, hepatitis C, HIV, tuberculosis) in high-risk populations or in countries with high tuberculosis burden (baseline). In addition, carriers and patients with evidence of current infection or recovery from prior hepatitis B infection should be monitored closely for clinical and laboratory signs of HBV reactivation and/or infection during therapy and for up to 2 years following completion of treatment. The American Society of Clinical Oncology HBV screening and management provisional clinical

	opinion recommends HBV screening with HBsAg, hepatitis B core antibody, total Ig or IgG, and antibody to hepatitis B surface antigen prior to beginning (or at the beginning of) systemic anticancer therapy; do not delay treatment for screening/results. Detection of chronic or past HBV infection requires a risk assessment to determine antiviral prophylaxis requirements, monitoring, and follow-up. Monitor for signs of active hepatitis B infection. - Monitor closely for infusion-related reactions, especially in patients with a history of prior cardiopulmonary reactions or with preexisting cardiac or pulmonary conditions or patients with high numbers of circulating malignant cells (≥25,000/mm3). Perform cardiac monitoring during and after rituximab infusion (in rheumatoid arthritis patients and in patients with preexisting cardiac disease, a history of arrhythmia or angina, or if clinically significant arrhythmias develop during or after subsequent infusions). Monitor for signs/symptoms of bowel obstruction/perforation (abdominal pain, vomiting), tumor lysis syndrome, and/or mucocutaneous skin reactions. Monitor for signs or symptoms of progressive multifocal leukoencephalopathy (focal neurologic deficits, which may

	present as hemiparesis, visual field deficits, cognitive impairment, aphasia, ataxia, and/or cranial nerve deficits); if progressive multifocal leukoencephalopathy is suspected, obtain brain MRI scan and lumbar puncture.
Precautions	- Herpes zoster reactivation: Herpes zoster reactivation has been reported. - Hyperlipidemia: Therapy is associated with increases in total cholesterol, triglycerides, low-density lipoprotein, and/or high-density lipoprotein. - Malignancy: Use of tocilizumab may affect defenses against malignancies; impact on the development and course of malignancies is not fully defined; however, malignancies were observed in clinical trials. - Demyelinating CNS disease: Use with caution in patients with preexisting or recent onset CNS demyelinating disorders; rare cases of CNS demyelinating disorders (multiple sclerosis and chronic inflammatory demyelinating polyneuropathy) have occurred. - Hepatic impairment: Use with caution in hepatic impairment; see "Dosage: Hepatic Function Impairment" for additional information. - Tuberculosis: Consider anti-tuberculosis (TB) treatment in patients with a history of latent or active TB infection or disease

	(latent or active TB) if adequate treatment course cannot be confirmed, and for patients with risk factors for TB despite a negative test.
Black Box Warning	Infusion-related reactions, mucocutaneous reactions, hepatitis B virus reactivation, progressive multifocal leukoencephalopathy
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *rituximab* for the treatment of grave's orbitopathy**. Despite this, ***rituximab*** has been available on the market for many years.

CONCLUSION STATEMENT – RITUXIMAB

Rituximab can be used as second-line therapy if the response to primary treatment is inadequate and Graves' orbitopathy remains at a moderate-to-severe and active stage as mentioned in the guidelines.

A double-blind, randomized trial was conducted to compare rituximab (RTX) with iv methylprednisolone (ivMP) in patients with active moderate to severe GO. The improved eye movement outcomes, the assessment of visual function quality of life, and the decreased need for surgical procedures in patients after receiving RTX indicate a potential disease-altering impact of the medication[15].

Furthermore, an open-label prospective study was conducted in which patients were treated with a single infusion of only 100 mg RTX to analyze the efficacy and safety of this low dose. The 100 mg dose of RTX proved to be effective for individuals with active moderate to severe Graves' orbitopathy (GO). Lower doses are better tolerated, result in a shorter duration of immune suppression for patients and offer a highly cost-effective alternative when compared to higher doses[14].

Therefore, it is recommended to add Rituximab to the SFDA list for this indication.

2.1.5 Azathioprine

This section includes pertinent information regarding the use of Prednisone (IMURAN®) in Grave's orbitopathy.

Table 21. Azathioprine Drug Information

SCIENTIFIC NAME **Azathioprine**	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	E.05
Drug Class	Immunosuppressant Agent
Drug Sub-class	Anti-CD20
ATC Code	L04AX01
Pharmacological Class (ASHP)	92:44 - Immunosuppressive Agents
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	Adjuvant therapy in severe Graves' disease: 1 mg/kg/day or 2mg/kg/day
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: **Altered kidney function:** - CrCl ≥30 mL/minute: Initial: No dosage adjustment necessary . - CrCl 10 to <30 mL/minute: Initial: Administer 75% to 100% of the usual indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to

	3 mg/kg once daily then administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended). - CrCl <10 mL/minute: Initial: Administer 50% to 100% of the usual indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended) . **Hemodialysis, intermittent (thrice weekly): Dialyzable (45% removed during 8 hours of hemodialysis):** Initial: Administer 50% to 100% of the indication-specific dose; if the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended). When scheduled dose falls on a dialysis day, administer after hemodialysis. If not administered after hemodialysis, provide a 50% supplemental dose. **Peritoneal dialysis:** Initial: Administer 50% to 100% of the indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended).

	CRRT: Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations are based on high-flux dialyzers and effluent flow rates of 20 to 25 mL/kg/hour (or ~1,500 to 3,000 mL/hour) unless otherwise noted. Close monitoring of response and adverse reactions (eg, hematologic toxicity) due to drug accumulation is important. Initial: Administer 75% to 100% of the indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended). **PIRRT (eg, sustained, low-efficiency diafiltration)**: Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection) and consideration of initial loading doses. Close monitoring of response and adverse reactions (eg, hematologic toxicity) due to drug accumulation is important. Initial: Administer 75% to 100% of the indication-specific dose. Administer the dose after PIRRT therapy ends on PIRRT days. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended)

	Hepatic Impairment: There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	ST, CU, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Should be used in combination with oral prednisone/prednisolone.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialty physician.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Considered as second line therapy if the response to primary treatment is inadequate and Graves' orbitopathy remains at a moderate-to-severe and active stage.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Nausea, vomiting, leukopenia, infection (renal transplant; rheumatoid arthritis ; includes bacterial infection, fungal infection, protozoal infection, viral infection, opportunistic infection, and reactivation of latent infections) - Most serious: Leukopenia, thrombocytopenia, hepatotoxicity, malignant lymphoma, hepatosplenic T-cell lymphoma (HSTCL), hemophagocytic lymphohistiocytosis (HLH), acute myelocytic leukemia, myelodysplastic syndrome, and malignant neoplasm of skin, pancreatitis.
Drug Interactions*	Risk X interactions: - Abrocitinib - Baricitinib

	- BCG (Intravesical) - BCG Products - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Dipyrone - Febuxostat - Fexinidazole - Filgotinib - Mercaptopurine - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib - Ruxolitinib (Topical) - Tacrolimus (Topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - Yellow Fever Vaccine
Special Population	Patients with systemic lupus erythematosus (SLE) undergoing hip or knee replacement surgery: Patients with severe SLE (referring to patients with severe organ manifestations such as nephritis) should not interrupt therapy when undergoing hip or knee replacement surgery. For patients with SLE without severe disease, hold azathioprine for at least 1 week prior to surgery to reduce infection risk; therapy can be restarted once surgical wound

	shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk)
Pregnancy	Azathioprine crosses the placenta. Adverse events, including congenital anomalies, immunosuppression, hematologic toxicities (lymphopenia, pancytopenia), and intrauterine growth retardation have been observed in case reports following maternal use in kidney allograft recipients. Some of these adverse outcomes may be dose-related or a result of maternal disease. Adverse pregnancy outcomes may also be associated with a kidney transplant, including preterm delivery and low birth weight in the infant and hypertension and preeclampsia in the mother. Appropriate maternal use of lower risk immunosuppressants may help decrease these risks. Azathioprine can be continued and should be substituted for mycophenolate in patients who become pregnant following a kidney transplant. Azathioprine may also be used in some pregnant patients who have had a liver, heart or uterine transplant. Although use for rheumatoid arthritis in pregnant patients is contraindicated by the manufacturer, available guidelines suggest that use of azathioprine may be acceptable for the management of rheumatic and musculoskeletal diseases during pregnancy. Patients with inflammatory bowel disease who are on maintenance

	therapy with azathioprine monotherapy may continue treatment during pregnancy; initiating treatment during pregnancy is not recommended. Combination therapy with azathioprine should be avoided due to increased risk of newborn infection. Treatment with azathioprine for autoimmune hepatitis should be continued during pregnancy. Because pregnancy may increase the risk of a flare, monitor closely for 6 months' postpartum. Azathioprine may also be useful for the treatment of immune thrombocytopenia in a pregnant patient refractory to preferred agents. Azathioprine is considered acceptable for the treatment of myasthenia gravis in pregnant patients who are not controlled with or unable to tolerate corticosteroids.
Lactation	The azathioprine metabolite 6-mercaptopurine (6-MP) is present in breast milk. Azathioprine is a prodrug which is rapidly metabolized to 6-MP. 6-MP is present in breast milk; however, it is inactive until further metabolized to 6-TGN metabolites which are present only within red blood cells. Peak breast milk concentrations of 6-MP occurred within 4 hours in a study of eight lactating women. Another study measured the active metabolite concentrations in RBCs of four breastfeeding women ≥3 months' postpartum on chronic azathioprine therapy; sampling was conducted at variable times after the dose. Women in the study had normal thiopurine methyltransferase (TPMT) activity. All

	women had therapeutic concentrations of 6-TGN; however, none of the infants had detectable concentrations. Newborn serum concentrations of 6-MP and 6-TGN were also undetectable in a study which evaluated seven breastfed infants between 1 and 28 days' postpartum. Mothers in this study were taking azathioprine 100 mg/day. Information is available from a report of 29 women taking azathioprine 50 to 175 mg/day throughout pregnancy and postpartum and their 30 breastfed newborns. Among 20 infants with blood cell counts evaluated after delivery, one infant was diagnosed with asymptomatic neutropenia on day 15 of life. Neutropenia fluctuated over 1.5 months of breastfeeding, continued for 15 days after breastfeeding was discontinued, and resolved 3.5 months later. No adverse outcomes were observed in the remaining infants who were followed for 1 to 17 months. A second study of 11 women taking azathioprine maintenance doses for inflammatory bowel disease (median: 150 mg/day) did not find an increased risk of infection in their 15 breastfed infants. The infants were followed for 6 months to 6 years. Recommendations for breastfeeding during azathioprine therapy vary. Due to the potential for serious adverse reactions in the infant, breastfeeding is not recommended by the manufacturer. The World Health Organization also recommends breastfeeding be avoided during maternal treatment.

	Recommendations for breastfeeding in females taking azathioprine following a kidney transplant differ; generally breastfeeding may be considered with maternal use of maintenance doses. Azathioprine is considered compatible for use in women with inflammatory bowel disease who wish to breastfeed. Azathioprine may be continued or initiated in patients with rheumatic and musculoskeletal diseases who are breastfeeding. Patients who are concerned with the theoretical risks of immunosuppression may consider pumping and discarding breast milk for the first 4 hours after an azathioprine dose to decrease potential exposure to the breastfed infant.
Contraindications	Hypersensitivity to azathioprine or any component of the formulation; pregnancy (in patients with rheumatoid arthritis [see Pregnancy Considerations]); patients with rheumatoid arthritis and a history of treatment with alkylating agents (eg, cyclophosphamide, chlorambucil, melphalan) may have a prohibitive risk of malignancy with azathioprine treatment.
Monitoring Requirements	- CBC with differential and platelets (weekly during first month, twice monthly for months 2 and 3, then monthly thereafter; monitor more frequently with dosage modifications or as clinically indicated), total bilirubin, LFTs (every 3 months), CrCl, monitor for signs/symptoms of infection and malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever,

	night sweats, weight loss). Azathioprine has been associated with skin cancer with long-term use after kidney transplantation. Patients taking azathioprine for a prolonged time period should avoid sun exposure and be monitored for skin cancer regularly. - Thiopurine S-methyltransferase (TPMT) genotyping or phenotyping: Consider testing for TPMT deficiency, particularly in patients with abnormally low CBC unresponsive to dose reduction. TPMT genotyping or phenotyping may assist in identifying patients at risk for developing toxicity (CPIC [Relling 2019]). - Nudix hydrolase 15 (NUDT15) genotyping: Consider genotyping for NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated myelosuppressive episodes. NUDT15 genotyping may assist in identifying patients at risk for developing toxicity (CPIC [Relling 2019]). - TPMT and NUDT15 testing cannot substitute for monitoring CBC in patients receiving azathioprine.
Precautions	- Hepatic impairment: Use with caution in patients with hepatic impairment. - Renal impairment: Use with caution in patients with renal impairment. - Mercaptopurine: Azathioprine is metabolized to mercaptopurine;

	concomitant use may result in profound myelosuppression and should be avoided. - Vaccines: Immune response to vaccines may be diminished. Toxicity or adverse reactions to live vaccines may be enhanced (depending on the azathioprine dose).
Black Box Warning	Malignancy
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *azathioprine* for the treatment of grave's orbitopathy**. Despite this, ***azathioprine*** has been available on the market for many years.

CONCLUSION STATEMENT – AZATHIOPRINE

Azathioprine can be used as second-line therapy in combination with oral prednisone/prednisolone if the response to primary treatment is inadequate and Graves' orbitopathy remains at a moderate-to-severe and active stage as mentioned in the guidelines.

Moreover, a randomized, open-label, and parallel-group clinical trial was conducted to investigate the effectiveness of AZA as an adjuvant therapy to antithyroid drugs (ATDs) for moderate and severe GD. In addition, an incremental cost-effectiveness analysis was done to determine its cost-effectiveness. By the end of follow-up, there was higher remission rate in the azathioprine groups compared with controls. Azathioprine may be a potential new, affordable, cost-effective, and safe medication that brings optimism for individuals with Graves' disease (GD) to attain prompt and enduring medical remission[16].

Therefore, it is recommended that azathioprine be added to the SFDA drug list for this indication.

2.2 Modifications

Metoprolol tartrate in the form of film-coated tablets should be added to the list since this dosage form was recently registered in the SFDA (2020).

2.3 Delisting

There are no drugs that should be delisted from the SFDA drug list.

2.4 Other Drugs

In January of 2020, Teprotumumab (Tepezza) was approved by the FDA for the treatment of THYROID EYE DISEASE in Graves' Disease patients[17].

Clinical trials:

Teprotumumab (TEPEZZA®) was assessed in two controlled clinical trials involving 171 patients diagnosed with Thyroid Eye Disease. These studies, referred to as Study 1 (NCT01868997) and Study 2 (NCT03298867), were both randomized, double-masked, and placebo-controlled. In these trials, patients were assigned randomly to receive TEPEZZA® or a placebo in a 1:1 ratio. The treatment regimen involved intravenous infusions, with the first infusion at a dosage of 10 mg/kg and the subsequent seven infusions at a dosage of 20 mg/kg, administered every 3 weeks, resulting in a total of 8 infusions. To be eligible for these studies, patients had to have a clinical diagnosis of Thyroid Eye Disease with associated symptoms and needed to be either euthyroid or have thyroxine and free triiodothyronine levels within 50% above or below the normal limits.

Study 1: "Teprotumumab for Thyroid-Associated Ophthalmopathy"[18]

The objective of the trial was to assess the efficacy and safety of teprotumumab, a human monoclonal antibody inhibitor of IGF-IR, in patients with active, moderate-to-severe ophthalmopathy. A total of 88 patients were randomly assigned to receive placebo or active drug administered intravenously once every 3 weeks for a total of eight infusions.

The primary end point was the response in the study eye. Therapeutic effects were rapid; at week 6, a total of 18 of 42 patients in the teprotumumab group (43%) and 2 of 45 patients in the placebo group (4%) had a response ($P<0.001$). Differences between the groups increased at subsequent time points.

As a conclusion, in individuals experiencing active ophthalmopathy, teprotumumab demonstrated superior effectiveness compared to a placebo in decreasing both proptosis and the Clinical Activity Score.

Study 2: "Teprotumumab for the Treatment of Active Thyroid Eye Disease"[19]

Patients with active thyroid eye disease were assigned in a 1:1 ratio to receive intravenous infusions of the IGF-IR inhibitor teprotumumab (10 mg per kilogram of body weight for the first infusion and 20 mg per kilogram for subsequent infusions) or placebo once every 3 weeks for 21 weeks; the last trial visit for this analysis was at week 24.

The primary outcome was a proptosis response (a reduction in proptosis of ≥2 mm) at week 24. A total of 41 patients were assigned to the teprotumumab group and 42 to the placebo group. At week 24, the percentage of patients with a proptosis response was higher with teprotumumab than with placebo (83% [34 patients] vs. 10% [4 patients], P<0.001), with a number needed to treat of 1.36.

As a conclusion, in individuals with active thyroid eye disease, teprotumumab led to more favorable results in terms of proptosis, Clinical Activity Score, diplopia, and quality of life compared to a placebo. Incidences of severe adverse events were infrequent.

The following information are retrieved from UpToDate[20]:

1. **Dosing:**

Thyroid eye disease: IV: 10 mg/kg as a single dose, followed by 20 mg/kg every 3 weeks for 7 additional doses.

2. **Main side effects:**

Most common: Alopecia, amenorrhea, diarrhea, nausea, dysmenorrhea, uterine hemorrhage, fatigue, muscle spasm

Most serious: Hearing impairment, hyperglycemia, infusion reactions

3. **Contraindications:**

There are no contraindications listed in the manufacturer's labeling.

4. **Warnings/ Precautions:**

Inflammatory bowel disease: Use may exacerbate preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease and discontinue use if IBD exacerbation is suspected.

Section 3.0 Key Recommendations Synthesis

- When dealing with potential hyperthyroidism in children, it is prudent to run examinations to measure the concentrations of free thyroxine (FT4), free triiodothyronine (FT3), and thyroid-stimulating hormone (TSH). Since Graves' disease (GD) stands as the primary root of hyperthyroidism, it is advisable to additionally carry out evaluations for anti-TSH receptor antibodies (TSHRAb, also known as thyroid-binding inhibitory immunoglobulin or TBII) and anti-thyroperoxidase antibodies (anti-TPO)[6].
- Individuals diagnosed with overt Graves' hyperthyroidism should undergo treatment using one of the following options: radioactive iodine (RAI) therapy, antithyroid drugs (ATDs), or thyroid surgery (thyroidectomy)[4].
- For young individuals with hyperthyroidism due to Graves' disease (GD), either carbimazole (CBZ) or its active form, methimazole (MMI), should be used. Propylthiouracil should be avoided (1,ØØØØ)[6].
- Patients who continue to experience thyrotoxicity despite being administered high doses of CBZ (carbimazole) at or above 1.3 mg/kg/day or MMI (methimazole) at or above 1 mg/kg/day should have conversations about alternative treatment possibilities, including surgical intervention or the use of radioactive iodine (RAI) (1,ØØØO)[6].
- Using beta-adrenergic blockers is recommended for patients who exhibit prominent symptoms of excessive thyroid hormone levels. They can be stopped once the patient achieves a state of biochemical euthyroidism (1,ØØØO)[6].
- When addressing hyperthyroidism, thiamazole and carbimazole are the preferred choices, except during the initial trimester of pregnancy or when pregnancy is anticipated (1/++)[5].
- The initial dose of antithyroid medications should be adjusted based on the severity of hyperthyroidism. The suggested starting doses are as follows: 40 mg daily for carbimazole and 30 mg daily for thiamazole when the FT4 levels are higher, typically exceeding 3-4 times the upper normal limit. If the FT4 levels are lower, the initial doses should be 20-30 mg of carbimazole or 15-20 mg of thiamazole (1/++)[5].
- Regardless of the chosen treatment protocol, the standard duration of treatment is typically 12–18 months (1/++)[5].
- If hyperthyroidism recurs after stopping antithyroid drug therapy, the treatment options (such as a second round of conventional antithyroid drugs or more decisive approaches like radioiodine therapy or surgery) should be

reviewed in consultation with the patient, considering their clinical condition. In certain circumstances, the possibility of prolonged, low dose antithyroid drug therapy may also be taken into consideration (2/+)[5].

- Before initiating radioiodine therapy, it is recommended to systematically start beta-blocker treatment in individuals experiencing symptomatic hyperthyroidism. This precaution is taken because there is a potential risk of temporary worsening of hyperthyroidism after radioiodine treatment, particularly when antithyroid drugs are not suitable or are not well tolerated (1/++)[5].
- Surgery is recommended when medical treatment fails or when complications arise (2/+)[5].
- The preferred primary approach is total thyroidectomy (1/+)[5].
- Alternatively, if the removal of the first thyroid lobe presents difficulties, partial thyroidectomy may be contemplated with the intention of minimizing the risk to recurrent nerves and parathyroid glands (2/+)[5].
- Pregnant women who are taking Methimazole (MMI) and need to continue treatment during pregnancy should be transitioned to Propylthiouracil (PTU) as soon as feasible (Weak recommendation, low-quality evidence)[10].
- In certain circumstances, thyroid surgery may be required during pregnancy. If it is deemed necessary, the optimal timing for thyroidectomy is generally during the second trimester of pregnancy. Nevertheless, if the mother exhibits a significantly elevated concentration of TRAb (more than three times the upper reference limit for the assay), close monitoring of the fetus for the potential development of fetal hyperthyroidism should be maintained throughout the pregnancy, even if the mother's thyroid function returns to normal following thyroidectomy (Strong recommendation, high-quality evidence)[10].
- Radioiodine therapy is contraindicated during pregnancy (1/++)[21].
- Fetal hyperthyroidism is managed through maternal antithyroid therapy (1/+)[21].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Hyperthyroidism report** and aims to provide recommendations to aid in the management of Hyperthyroidism. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Hyperthyroidism. Health professionals are expected to consider this guidance

alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Hyperthyroidism Scope

2020	Changes	2023	Rationale
Section 1.0 Hyperthyroidism Clinical Guidelines			
Thyroid disease: assessment and management NICE guideline Published: 20 November 2019		NICE Guideline on Assessment and Management of Thyroid Disease (Published 2019, Updated 2023)[8]	**Managing thyrotoxicosis** **Tests for people with confirmed thyrotoxicosis: Adults and children and young people** **Initial treatment in primary/non-specialist care** **Initial treatment in secondary/specialist care** **Adults with Graves' disease** **Adults with toxic nodular goitre** **Children and young people with Graves' disease or toxic nodular goitre** **Antithyroid drugs for adults, children and young people with hyperthyroidism**
2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism	N/A		
2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism	N/A		

and Other Causes of Thyrotoxicosis			
	Missing	2022 European Thyroid Association Guideline for the management of pediatric Graves' disease[6]	• In the case of suspected hyperthyroidism in pediatric patients, it is advisable to conduct tests for serum levels of free thyroxine (FT4), free- triiodothyronine (FT3), and thyroid-stimulating hormone (TSH). Given that Graves' disease (GD) is the most common underlying cause of hyperthyroidism, it is recommended to also perform assessments for anti-TSH receptor antibodies (TSHRAb, also referred to as thyroid-binding inhibitory immunoglobulin or TBII) and anti-thyroperoxidase antibodies (anti-TPO). **Medical treatment of hyperthyroidism caused by Graves' disease (GD)** • In pediatric patients suspected of having hyperthyroidism, it is advisable to promptly initiate treatment (1,ØØØØ). • For young individuals with hyperthyroidism due to Graves' disease (GD), either carbimazole (CBZ) or its active form, methimazole (MMI), should be used. Propylthiouracil should be avoided (1,ØØØØ). • The initial dosage of antithyroid drugs (ATDs) should range from 0.15 to 0.5 mg/kg for MMI or 0.25 to 0.75 mg/kg for CBZ, given once daily (1,ØØØO). • When employing a dose titration (DT) approach, most patients achieve normalized thyroid hormone levels within the initial 4–6 weeks with a starting dose of 0.15–0.3 mg/kg for MMI or 0.25–0.5 mg/kg for CBZ. Dose reductions of 25–50% based on thyroid function tests

			are recommended, and higher ATD doses may be considered for severe cases (1,ØØØO). • Treatment adjustments may not be necessary if FT4 or FT3 levels are relatively high and TSH remains within the normal range (1,ØOOO). • Educating patients about GD and its treatment is essential to enhance compliance, taking into account their developmental stage (1,ØØOO). • In the block and replace (BR) strategy, a dose of 0.3–0.5 mg/kg for MMI or 0.5–0.75 mg/kg for CBZ effectively inhibits endogenous thyroid hormone production. Levothyroxine can be introduced at an age and weight-appropriate replacement dose once FT3 levels fall within the reference range. Higher ATD doses may be required if thyroid hormone concentrations, particularly FT3, do not decrease as expected (1,ØØØO). • In most cases, a dose titration (DT) approach is the preferred method for ATD treatment (1,ØØØO). • It is advisable to use beta-adrenergic blockade in patients presenting with pronounced signs of excess thyroid hormone. This can be discontinued once the patient attains biochemical euthyroidism (1,ØØØO). • Patients with untreated GD may experience severe illness characterized by prominent signs of thyroid hormone excess, necessitating management in a high dependency or intensive care unit (1,ØØØO). • Patients managed with DT or BR should undergo evaluations approximately every 4 weeks during the initial 3 months, transitioning to 2 and subsequently 3-

			month assessments depending on the clinical course (1,ØØØO). • Baseline assessments, including white blood cell count, neutrophil count, and liver function tests, should be conducted because both can be influenced by the underlying disease process and ATD therapy (1,ØØØO). • Thyroid hormone concentrations (FT4 and FT3) should typically normalize within the first 6 weeks, with noticeable improvement in the initial 4 weeks. TSH suppression may persist for several months (1,ØØØO). • Families should be cautioned about the potential for excessive weight gain during ATD therapy (1,ØØØO). • Minor side effects of ATDs occur in 10 to 20% of patients and are generally transient. Serious side effects warranting ATD discontinuation are rare (1,ØØØO). • Patients and families should receive counseling regarding ATD side effects and the criteria for discontinuing the drug and seeking guidance from healthcare professionals (1,ØØØØ). • For patients who remain thyrotoxic despite receiving large doses of CBZ (≥1.3 mg/kg/day) or MMI (≥1 mg/kg/day), alternative treatment options such as surgery or radioactive iodine (RAI) should be discussed (1,ØØØO). • Definitive treatment (total thyroidectomy or RAI) should be considered for patients who develop severe neutropenia, significant liver dysfunction, troublesome

			side effects that do not resolve, or when prolonged ATD therapy has not resulted in remission. It may also be appropriate when patients cannot accurately report potential ATD side effects or face compliance issues (1,ØØØØ). • TSH receptor antibodies (TSHRAb) can be utilized to predict the likelihood of remission. Elevated TSHRAb levels indicate a low probability of remission, and discontinuing ATD therapy is not recommended (1,ØØØO). • Typically, ATD treatment is administered for at least 3 years and should be discontinued only when TSHRAb levels have consistently been low for several months. Longer courses of ATD treatment (≥5 years) may be considered in cases where the likelihood of remission is low based on initial disease characteristics (1,ØØØO). • The overall remission rate in pediatric GD patients after 2 years of ATD treatment is approximately 20-30% and may increase with continued ATD therapy (1,ØØØØ). • When discontinuing ATD treatment, it is important to discuss the signs of thyroid hormone excess and establish a pathway for thyroid function testing (1,ØØØO). • Patients who experience a relapse after completing a course of ATD treatment can choose to either resume ATD therapy or opt for definitive treatment. This decision may be influenced by factors such as age or educational stage (1,ØØØO).

			• There is currently no established role for immune modulation using new agents like biologics in young individuals with GD (1,ØØØO). **Definitive treatment in pediatric GD – radioiodine (RAI)** • The primary aim of radioactive iodine (RAI) treatment (I-131) is to achieve complete thyroid ablation, a critical step to prevent both relapse and the potential development of thyroid cancer (1,ØØOO). • It is advisable to avoid administering RAI to patients younger than 5 years old. However, for the age group between 5 and 10 years, RAI may be considered when surgery is not a feasible option. There are no contraindications to using RAI in patients older than 10 years or post-pubertal children (1,ØØOO). • Ideally, RAI activity should be customized based on individual needs. When dosimetry calculations are challenging, a recommended activity is 15 MBq (0.4 miCi) per gram of thyroid tissue. Alternatively, when dosimetry is available, the aim should be to deliver at least 300 Gy to the thyroid gland. To calculate the I-131 dose accurately, thyroid weight is best estimated using ultrasound (2,ØØØO). • Prior to undergoing RAI treatment, it is important to discontinue antithyroid drugs (ATD) for a period of 3–7 days (1,ØØØO). • The administration of RAI therapy should be avoided if a patient presents with active Graves' orbitopathy (GO). In cases of inactive GO, it is recommended to

			concurrently provide a course of steroids to prevent relapse or exacerbation (1,ØØØØ). **Definitive treatment in pediatric Graves' disease – thyroidectomy** • Pediatric patients scheduled for thyroidectomy should be operated on by a highly experienced thyroid surgeon with a significant case volume (1,ØØØØ). • The preferred surgical approach for pediatric patients is total thyroidectomy (1,ØØØO). • Prior to surgery, it is crucial for pediatric patients with Graves' disease (GD) to achieve a state of biochemical euthyroidism. This may require pre-operative treatment with antithyroid drugs (ATDs), and if necessary, iodine, a beta-blocker, and glucocorticoid (1,ØØØØ). • Administering pre-operative vitamin D treatment reduces the risk of transient post-operative hypocalcemia in those who are deficient in vitamin D (2,ØØOO). • Initiation of levothyroxine treatment should commence shortly after thyroidectomy in pediatric patients (1,ØØOO). **Management of pediatric Graves' orbitopathy** • Children displaying eye-related symptoms should seek consultation with an orbital specialist, preferably within combined thyroid eye clinics staffed by both ophthalmologists and physicians (1,ØØØO). • Mild symptoms of Graves' orbitopathy (GO) lacking inflammatory features can either be observed over

			time or, when deemed necessary, managed with selenium supplementation (2,ØØOO). • In the rare instances of moderate to severe active GO cases, treatment options may include anti-inflammatory medications, such as intravenous corticosteroids (1,ØØOO). • Chronic, stable, and inactive GO cases, which can adversely affect the patient's quality of life, can be considered for surgical interventions similar to those in adults. However, except for decompression surgery, these surgical procedures should be postponed until the facial skull has reached full growth (1,ØØOO). **Management of an increased thyroid cancer risk** • Similar to adults, young patients diagnosed with Graves' disease (GD) may face a slightly elevated risk of developing differentiated thyroid cancer (2,ØØOO). • Children and adolescents with GD who present with a detectable thyroid nodule should receive care from a pediatric endocrinologist working in conjunction with a relevant multidisciplinary team (2,ØOOO). • Young patients with a thyroid nodule or nodules should undergo either a thyroid ultrasound examination followed by cytological evaluation if suggested by the sonographic findings or consider total thyroidectomy (2,ØØOO). **Prognosis** • Young individuals who are diagnosed with Graves' disease (GD) during childhood and receive treatment may experience a reduced quality of life compared to

			their healthy peers. It is important to be mindful of this potential impact and, when deemed necessary, implement suitable measures to address and improve their well-being (1,ØØOO).
	Missing	Consensus on the Treatment of adult Graves' disease (2018)[5]	• The decision regarding the treatment for Graves' disease should be a collaborative process involving the patient. After providing a thorough explanation of the advantages and disadvantages of the three traditional treatment options, it is essential to seek the guidance of a specialist. They will help select the most suitable treatment and establish a monitoring plan (1/++). • Regardless of the selected treatment approach, an appropriately adjusted dosage of antithyroid drugs should be prescribed initially to achieve a state of euthyroidism (1/++). • To manage hyperthyroidism, thiamazole and carbimazole are preferred over propylthiouracil, except during the first trimester of pregnancy or if there are plans for pregnancy (1/++). • Regarding antithyroid drugs, there is a lack of strong evidence supporting or opposing the routine monitoring of blood counts during treatment. However, if blood-count monitoring is initiated, it is advisable to commence with a pre-treatment blood count (2/++). • In the event of symptoms of infection or the onset of pharyngitis during antithyroid drug treatment, an immediate blood count should be conducted. If the polymorphonuclear neutrophil count falls below

			800/mm3, it necessitates discontinuation of antithyroid treatment and definitively prohibits the reintroduction of thionamides (1/+++). • Due to the risk of severe hepatitis, propylthiouracil (PTU) should be reserved for specific cases, including pregnancy or plans for pregnancy, minor thiamazole allergy, and situations involving iodine overload. There is no strong evidence either in favor of or against routine monitoring of transaminase levels. However, if clinical and/or severe hepatitis occurs (with transaminase levels exceeding 3 times the upper normal limit), it necessitates discontinuation of antithyroid treatment (1/++). • There is limited strong evidence supporting the routine monitoring of anti-neutrophil antibodies. (2/+). • Patients should receive comprehensive information, preferably in written form, regarding potential minor and major side effects of antithyroid treatment, as well as the initial symptoms to watch for and the appropriate steps to take if these symptoms arise. (1/++). • The initial dosage of antithyroid drugs should be tailored to the severity of hyperthyroidism. The recommended starting doses are as follows: 40 mg daily for carbimazole and 30 mg daily for thiamazole if the FT4 concentration exceeds 3–4 times the upper limit of normal. For lower FT4 concentrations, initial doses should be 20–30 mg of carbimazole or 15–20 mg of thiamazole (1/++).

			• Both the "adapted" and "combined" treatment protocols demonstrate equal efficacy. The decision regarding which protocol to choose is left to the clinician, who should consider their usual practice and take into account the patient's preference (No recommendations. No evidence in favor of one or other protocol) • Regardless of the chosen treatment protocol, the standard duration of treatment is typically 12–18 months (1/++). • During the euthyroid recovery phase, hormonal monitoring of antithyroid treatment primarily involves assessing FT4 ± FT3 levels. This monitoring should occur at least monthly until the patient reaches a state of euthyroidism, defined as the normalization of FT4 ± FT3 levels. It's important to note that TSH may remain below the normal range for one month or more even after thyroid function has normalized, so it serves as a secondary indicator of euthyroid status (1/++). • After achieving euthyroid status and the normalization of TSH levels, hormonal monitoring of antithyroid treatment should include TSH and FT4 assessments at appropriate intervals. For adapted dose treatment, monitoring should occur at least every 2 months, while for combined treatment, it should be conducted every 4 months. The intervals can be adjusted if there are changes in the dosage or if results are unstable (1/++). • At the conclusion of the standard treatment course, it is advisable to conduct an Anti-thyroid stimulating

			hormone receptor (anti-TSH-R) antibody assay to evaluate the risk of recurrence following treatment (1/++). • If hyperthyroidism reoccurs after discontinuation of antithyroid drug treatment, the treatment choices (such as a second course of traditional antithyroid drugs or more definitive approaches like radioiodine therapy or surgery) should be reevaluated through discussion with the patient, considering the clinical information. In specific situations, the option of extended-duration, low-dose antithyroid drug treatment may also be considered (2/+). • In elderly patients experiencing symptomatic hyperthyroidism and in any patient with a resting heart rate exceeding 90–100 beats per minute, beta-blockers can be employed if there are no contraindications. Additionally, they can be considered for symptom relief in all individuals with symptoms related to hyperthyroidism (1/++). • Prior to administering radioiodine, it is advisable to initiate beta-blocker treatment systematically in individuals with symptomatic hyperthyroidism. This precaution is taken due to the potential risk of transient exacerbation of hyperthyroidism following radioiodine treatment, especially when antithyroid drugs are contraindicated or not well tolerated (1/++). • Medical preparation using antithyroid drugs can be beneficial when it is not contraindicated or not well tolerated, particularly in fragile patients (such as the

			elderly, those with severe symptoms, those with elevated thyroid hormone levels, or those with a cardiovascular history). If prescribed, antithyroid treatment should be temporarily discontinued for a period of 3–7 days surrounding the radioiodine treatment. However, there is no consensus on the optimal duration for this interruption (2/++). • In the case of Graves' disease, an "ablative" approach is more suitable than a "dose-adjustment" approach when using radioiodine therapy. The radioiodine dose administered should be sufficient to induce hypothyroidism (1/++). • There is no preference for a specific method to determine the radioiodine dose; both fixed and dose-adjusted methods can be employed. However, fixed or semi-fixed dose methods are advantageous due to their simplicity. (No specific recommendation; no grading provided). • Regardless of the chosen dose determination method, it is essential to conduct thyroid ultrasound and scintigraphy imaging assessments. Ultrasound is used to characterize any nodules and measure thyroid volume. Scintigraphy, utilizing iodine-123 or technetium-99m, measures thyroid uptake under the same conditions as the actual treatment, with the potential interruption of antithyroid drugs if necessary (1/++).

			• In women of child-bearing age, a pregnancy test should be conducted no later than 72 hours before administering iodine-131 treatment (1/++). • Breastfeeding should be permanently discontinued at least 4 weeks before undergoing treatment (1/++). • Following treatment, effective contraception should be maintained for a duration of 6 months (1/++). • After ablative radioiodine treatment, it is recommended to measure TSH and FT4 levels at 4 weeks post-treatment and subsequently every 4–6 weeks for a total duration of 6 months. Specialist consultation during this period is essential to ensure appropriate hormone replacement therapy and prevent complications related to severe hypothyroidism. Additionally, during this consultation, the orbital status can be assessed (1/+++). • Once hormonal balance has been successfully restored, it is necessary to undergo an annual TSH assay, with no specified time limit for its continuation (1/+++). • Treatment failure is characterized by the presence of persistent hyperthyroidism 6–12 months following radioiodine treatment (1/+++). • In the event of treatment failure, a second treatment may be considered, with the precaution of avoiding excessively low doses, which should not be less than 5–10 mCi or 185–370 MBq (2/++). • Radioiodine treatment carries a risk of exacerbating pre-existing orbitopathy or inducing new orbitopathy,

			particularly in individuals who smoke. While radioiodine is not strictly contraindicated for individuals with orbitopathy, its use should be limited to cases of mild or moderately inactive orbitopathy. Specific precautions should be taken, including patient education, strong encouragement to cease smoking, consultation with an ophthalmology specialist, oral corticosteroid therapy, and vigilant monitoring to prevent the development of hypothyroidism (1/+++). • There is a lack of evidence supporting routine levothyroxine replacement therapy following treatment in patients with risk factors such as smoking or high TSH-R antibody levels but without orbitopathy. • In individuals at a high risk of orbitopathy or those with mild or inactive orbitopathy, thyroid function should be evaluated through free T4 and TSH measurements within 2 weeks of receiving radioiodine treatment (1/++). • Before undergoing radioiodine treatment, it is recommended to conduct fine-needle aspiration in any thyroid nodule larger than 1 cm and those deemed suspicious based on ultrasound findings (1/+++). • Radioiodine treatment may also be considered for cytologically benign nodules (1/++). • Follow-up procedures should be similar to those typically conducted for thyroid nodules (1/++). • Surgery is not the initial treatment of choice for Graves' disease (1/+).

			• Surgery is recommended when medical treatment fails or when complications arise (2/+). • Surgery should be carried out when the patient is in a euthyroid state (1/++). • Surgery should be conducted in a specialized center or a center with extensive experience in thyroid surgery (1/++). • Total thyroidectomy is the preferred initial approach (1/+). • Alternatively, if the dissection of the first thyroid lobe is challenging, subtotal thyroidectomy can be considered with the aim of reducing the risk to recurrent nerves and parathyroid glands (2/+). • There are no specific recommendations for the preoperative application of Lugol's iodine to reduce complication rates (2/+). • The use of Lugol's iodine is at the discretion of the surgeon (2/+).
	Missing	Consensus on Graves' disease and pregnancy (2018)[7]	• It is important to maintain normal thyroid parameter values according to the trimester of pregnancy and reference values established for pregnancy (1/+++). • The diagnosis of hyperthyroidism during pregnancy should rely on TSH and free T4 measurements, with interpretation considering the normal physiological changes that occur during pregnancy (1/+++). • The diagnosis of Graves' disease should be based on the assessment of anti-TSH-R antibodies (1/+++).

			• In cases of hyperemesis gravidarum, it is necessary to evaluate thyroid function through TSH and free T4 measurements to assess thyroid dysfunction (1/++). • Thyroid scintigraphy is not recommended during pregnancy due to contraindications (1/++). • When maternal hyperthyroidism is confirmed, characterized by an elevated free T4 concentration, it should be treated and corrected (1/+++). • The treatment of subclinical hyperthyroidism, which is defined as isolated low TSH concentration, is not recommended (1/+++). • Treatment of Graves' disease during pregnancy primarily involves the use of antithyroid drugs. Levothyroxine, due to its limited placental transfer, is recommended using the adapted-dose strategy. If combined treatment (levothyroxine and antithyroid drugs) was employed before pregnancy, it's essential to discontinue levothyroxine and continue with antithyroid drugs at the adapted dose (1/+++). • There have been reports of malformations associated with in utero exposure to imidazole-derivative antithyroid drugs and, to a lesser extent, propylthiouracil. Propylthiouracil is also associated with rare but severe cases of hepatitis. Therefore, it is recommended to prescribe propylthiouracil during the first trimester of pregnancy and then switch to an imidazole-derivative. However, switching during pregnancy can disrupt thyroid balance and requires closer monitoring. If significant improvement in

			hyperthyroidism allows for dose reduction or discontinuation of antithyroid drugs during pregnancy, continuing propylthiouracil may be considered (1/++). • If there is a switch of antithyroid drugs during pregnancy, thyroid monitoring should be intensified (1/++). • Surgery is an option when there is an allergy to antithyroid drugs or when maternal hyperthyroidism is poorly controlled. Surgery is preferably performed during the second trimester (1/++). • Radioiodine therapy is contraindicated during pregnancy (1/++). • Treatment of Graves' disease during pregnancy should adhere to the adapted-dose strategy (1/++). • Monitoring of antithyroid treatment during pregnancy should be rigorous, with assessments initially conducted every 2 weeks and then every 2–4 weeks depending on the progression (1/++). • Monitoring of antithyroid treatment during pregnancy relies on free T4 and TSH assays. TSH levels may remain low, while free T4 levels should be maintained in the upper range of normal (1/++). • If, at the minimum antithyroid dose, the clinical condition is satisfactory and maternal free T4 levels decrease in two successive assays, discontinuation of treatment may be considered (2/++). • Although there is no conclusive evidence, it is recommended to monitor transaminase levels every 2–4 weeks during propylthiouracil treatment during

			pregnancy. Patients should be advised to avoid other hepatotoxic drugs and to seek medical attention in case of digestive symptoms (2/+). • Women of child-bearing age who have Graves' disease should receive information about the fetal risks associated with the condition and the management of hyperthyroidism during pregnancy (1/+++). • Pregnancy should be avoided for at least 6 months following radioiodine therapy (1/++). • In cases where radical therapy is being considered and there is a pregnancy plan, total thyroidectomy may be a preferable option over radioiodine treatment because it leads to a faster decrease in anti-TSH-R antibody levels (2/++). • Fetuses of mothers with Graves' disease can potentially develop hyperthyroidism due to the passage of anti-TSH-R antibodies across the placenta, or hypothyroidism due to the passage of antithyroid drugs (1/++). • The presence of a goiter in the fetus is the most effective sign of fetal thyroid dysfunction and can be detected through standardized ultrasound measurements based on gestational age (1/+++). • Fetal hyperthyroidism may be suspected when there are signs such as fetal goiter, delayed intrauterine growth, and fetal tachycardia (which is a late sign of severe hyperthyroidism) (1/++). • The goal of treatment is to prevent fetal hyperthyroidism through early detection of fetal

			thyroid hypertrophy and appropriate adjustment of maternal treatment. Additionally, the aim is to prevent fetal hypothyroidism resulting from antithyroid drug overdose or unjustified combination with levothyroxine. (The combination of maternal treatments is contraindicated.) (1/++). • Effective treatment of fetal thyroid dysfunction is crucial to prevent premature mortality and long-term neurological complications (1/+++). • Anti-TSH-R antibody testing should be conducted at the beginning of pregnancy, and if these antibodies are present, monitoring should be intensified (1/+++). • If the concentration of anti-TSH-R antibodies is > 5 IU/L as per the 2nd generation assay in the 2nd trimester, it indicates a risk of fetal and neonatal hyperthyroidism. In such cases, ultrasound monitoring should be intensified, with monthly fetal ultrasounds starting from 22 weeks' amenorrhea. The monitoring frequency should be adjusted based on the appearance of fetal thyroid hypertrophy (1/++). • Because the quality of fetal thyroid ultrasound scans depends on the operator, it is advisable for both the mother and fetus to be monitored in a multidisciplinary expert center (1/++). • Fetal goiter is defined by dimensions that exceed the 95th percentile based on gestational age (1/+++). • Fetal blood sampling should only be considered in cases of fetal goiter when non-invasive assessments or treatment adjustments fail to determine fetal thyroid

			functional status. The decision to proceed with fetal blood sampling should be confirmed by a multidisciplinary prenatal diagnostic center (1/++). • Prenatal treatment has been found effective in correcting fetal and neonatal thyroid dysfunction. • In cases of fetal hypothyroidism due to maternal antithyroid therapy, the maternal dose of antithyroid drugs should be reduced (1/++). • For persistent hypothyroidism in the fetus despite appropriate maternal treatment, intra-amniotic administration of levothyroxine may be considered. This decision should follow confirmation by fetal blood sampling, which needs validation by a multidisciplinary prenatal diagnostic center (2/+). • Fetal hyperthyroidism is managed through maternal antithyroid therapy (1/+). • In cases where anti-TSH-R antibodies are present during pregnancy, there is a risk of neonatal hyperthyroidism, particularly when antibody levels exceed 5 IU/L on the 2nd generation assay (1/+++). • Umbilical blood should be systematically tested for TSH, free T4, and anti-TSH-R antibodies if the mother has anti-TSH-R antibodies or is on antithyroid drugs during pregnancy. These tests provide information about the prenatal status and/or treatment and guide postnatal monitoring (1/++). • Neonatal hyperthyroidism is not a risk when anti-TSH-R antibodies were absent in the mother throughout pregnancy (1/++).

			• High levels of anti-TSH-R antibodies in umbilical blood are associated with a significant risk of neonatal hyperthyroidism. Monitoring should continue, involving collaboration with a pediatric endocrinologist (1/++). • Normal thyroid hormone levels (TSH and free T4) in umbilical blood at delivery do not predict neonatal hyperthyroidism (1/++). • A rapid increase in free T4 levels beyond the age-related upper limit of normal between umbilical sampling and 3-5 days after birth is indicative of neonatal hyperthyroidism (1/++). • Carbimazole treatment should be initiated at a dose of 0.5 mg/kg/day when biological signs of neonatal hyperthyroidism are observed, considering age-related normal values. Propranolol may be added if there are clinical signs. • In cases of neonatal hyperthyroidism, carbimazole treatment should be continued until anti-TSH-R antibodies become negative (1/++). • Low free T4 levels at birth, accompanied by low or non-elevated TSH levels, require monitoring in collaboration with a pediatric endocrinologist (2/++). • There is inadequate evidence to suggest that maternal hyperthyroidism during pregnancy has any significant impact on the intellectual, psychological, or behavioral development of children and young adults (1/++). • Currently, it is advisable to maintain free T4 levels within the normal range in women receiving

			treatment for Graves' disease during pregnancy (1, and expert opinion / ++).
	Missing	2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum[10]	• If a suppressed serum TSH level is identified during the first trimester (TSH lower than the reference range), it is recommended to conduct a thorough medical history, physical examination, and measure maternal serum FT4 or TT4 concentrations. In certain cases, measuring TRAb (thyroid receptor antibodies) and maternal TT3 (total triiodothyronine) levels may be beneficial in determining the cause of thyrotoxicosis (Strong recommendation, moderate-quality evidence). • Radionuclide scintigraphy or radioiodine uptake measurements should be avoided during pregnancy (Strong recommendation, high-quality evidence). • The appropriate management of abnormal maternal thy-roid tests attributable to gestational transient thyrotoxicosis and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed. ATDs are not recommended, though b-blockers may be considered (Strong recommendation, moderate-quality evidence). • All women of childbearing age who experience thyrotoxicosis should engage in discussions about the potential for future pregnancy. Specifically, women with Graves' disease (GD) who plan to become pregnant should receive counseling regarding the challenges of managing the condition during pregnancy, including the potential risks of birth

			defects associated with the use of antithyroid drugs (ATDs). Preconception counseling should encompass a thorough review of the risks and advantages of various treatment options, as well as consideration of the patient's desired timing for conception (Strong recommendation, high-quality evidence). • Women with thyrotoxicosis should aim to achieve a stable euthyroid state before attempting pregnancy. There are various treatment options available, each carrying its own set of advantages and disadvantages. These options include radioactive iodine (131I) ablation, surgical thyroidectomy, or antithyroid drug (ATD) therapy. It's important to carefully consider these treatment choices in light of their potential risks and benefits, particularly in the context of future pregnancy plans (Strong recommendation, moderate-quality evidence). • Women who are taking either Methimazole (MMI) or Propylthiouracil (PTU) should be advised to promptly confirm the possibility of pregnancy as soon as they suspect it. If a pregnancy test yields a positive result, it is crucial for pregnant women to get in touch with their healthcare provider without delay to ensure appropriate management and guidance during pregnancy (Strong recommendation, high-quality evidence) • In the case of a newly pregnant woman with Graves' disease (GD) who is currently on a low dose of either Methimazole (MMI) (≤5–10 mg/day) or Propylthiouracil (PTU) (≤100–200 mg/day), the healthcare provider

			should consider the possibility of discontinuing the antithyroid medication due to potential teratogenic effects. The decision to stop the medication should be based on various factors, including the patient's medical history, the size of the goiter, the duration of therapy, recent thyroid function test results, measurement of TRAb (thyrotropin receptor antibodies), and other clinical considerations (Weak recommendation, low-quality evidence). • Following the discontinuation of antithyroid medication, maternal thyroid function testing (including TSH, and FT4 or TT4) and clinical examinations should be conducted every 1–2 weeks to assess both maternal and fetal thyroid status. If the pregnant woman remains clinically and biochemically euthyroid, the testing intervals may be extended to 2–4 weeks during the second and third trimesters (Weak recommendation, low-quality evidence). • At each assessment, the decision to continue conservative management (withholding antithyroid medication) should be made based on both the clinical and biochemical evaluation of maternal thyroid status (Weak recommendation, low-quality evidence). • In pregnant women at high risk of developing thyrotoxicosis if antithyroid drugs were to be discontinued, it may be necessary to continue antithyroid medication. Factors that predict a high clinical risk include current hyperthyroidism or the

			need for >5–10 mg/day MMI or >100–200 mg/day PTU to maintain a euthyroid state. In such cases: • Propylthiouracil (PTU) is strongly recommended for treating maternal hyperthyroidism through 16 weeks of pregnancy (Strong recommendation, moderate-quality evidence). • Pregnant women who are receiving Methimazole (MMI) and require ongoing therapy during pregnancy should be switched to PTU as early as possible (Weak recommendation, low-quality evidence). • When transitioning from MMI to PTU, a dose ratio of approximately 1:20 should be used (e.g., MMI 5 mg/day = PTU 50 mg twice daily) (Strong recommendation, moderate-quality evidence) • If antithyroid drug therapy is needed after 16 weeks of gestation, it remains unclear whether PTU should be continued or if therapy should be changed to MMI. Both medications have potential adverse effects, and switching between them may result in a period of less tightly controlled thyroid function. Therefore, no specific recommendation regarding switching antithyroid drug medication can be made at this time (No recommendation, insufficient evidence). • Pregnant women receiving antithyroid drugs (ATDs) should undergo regular monitoring of FT4/TT4 and TSH levels approximately every 4 weeks (Strong recommendation, moderate-quality evidence). • During pregnancy, antithyroid medication should be prescribed at the minimal effective dosage of either

			Methimazole (MMI) or Propylthiouracil (PTU), with the objective of maintaining maternal serum FT4/TT4 levels at or slightly above the upper limit of the reference range (Strong recommendation, high-quality evidence). • The combination of levothyroxine (LT4) and ATD) should generally be avoided during pregnancy, except in rare cases of isolated fetal hyperthyroidism (Strong recommendation, high-quality evidence). • Thyroidectomy during pregnancy may be necessary in specific situations. If deemed necessary, the best timing for thyroidectomy is typically during the second trimester of pregnancy. However, if the mother has a high concentration of TRAb (>3 times the upper reference limit for the assay), close monitoring of the fetus for the development of fetal hyperthyroidism should continue throughout the pregnancy, even if the mother's thyroid function is normal after thyroidectomy (Strong recommendation, high-quality evidence). • We agree with the consensus guidelines from the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, as stated in 2011 and revised in 2015: • A pregnant woman should never be denied necessary surgery, regardless of the trimester. • Elective surgery should be postponed until after delivery.

			• If feasible, non-urgent surgery should be scheduled during the second trimester of pregnancy when the risk of preterm contractions and spontaneous abortion is lower. • In cases where a patient with Graves' disease requires urgent non-thyroid surgery and is well controlled on antithyroid drugs (ATDs), no additional preparation is typically needed. Beta-blockers may also be used if necessary (Strong recommendation, moderate-quality evidence) • If a pregnant woman has a previous history of Graves' disease treated with thyroid ablation (radioiodine or surgery), it is strongly advised to have a maternal blood test to check TRAb levels as part of the initial thyroid function assessment in early pregnancy. (Strong recommendation, moderate-quality evidence) • If the initial TRAb test in early pregnancy shows elevated levels, it is strongly recommended to repeat the TRAb testing between weeks 18 and 22 of pregnancy (Strong recommendation, moderate-quality evidence). • If the initial TRAb test in early pregnancy indicates undetectable or low TRAb levels, further TRAb testing is not necessary (Weak recommendation, moderate-quality evidence). • If a patient is already taking antithyroid drugs (ATDs) to manage Graves' hyperthyroidism when pregnancy is confirmed, it is weakly recommended to perform a

			maternal blood test to measure TRAb levels (Weak recommendation, moderate-quality evidence). • If the patient continues treatment with ATDs for Graves' disease up to mid-pregnancy, it is strongly recommended to repeat the TRAb test between weeks 18 and 22 (Strong recommendation, moderate-quality evidence). • If elevated TRAb levels are detected between weeks 18 and 22 or if the mother is still taking ATDs in the third trimester, another TRAb measurement should be conducted in late pregnancy (between weeks 30 and 34). This is essential to assess the need for monitoring the newborn and postnatal care. (Strong recommendation, high-quality evidence). • Fetal monitoring is advisable for pregnant women with poorly managed hyperthyroidism in the latter half of pregnancy and for those who exhibit elevated TRAb levels at any point during pregnancy (exceeding three times the upper normal limit). It is recommended to consult with an experienced obstetrician or a specialist in maternal-fetal medicine for this purpose. The monitoring process may involve the use of ultrasound to evaluate fetal heart rate, growth, amniotic fluid levels, and the potential presence of fetal goiter. (Strong recommendation, moderate-quality evidence). • Cordocentesis should only be employed in exceptional situations and should be conducted in a suitable medical environment. In some rare instances, when fetal goiter is identified in pregnant women

			undergoing ATD treatment, cordocentesis may be considered to assist in determining whether the fetus is experiencing hyperthyroidism or hypothyroidism (Weak recommendation, low-quality evidence). • If ATD treatment is prescribed for hyperthyroidism resulting from autonomous nodules, it is crucial to closely observe the fetus for the development of goiter and signs of hypothyroidism in the latter half of pregnancy. A minimal ATD dose should be administered with the objective of maintaining the maternal FT4 or TT4 levels at or slightly above the upper limit of the reference range (Strong recommendation, low-quality evidence). • The effect of maternal hyperthyroidism on breastfeeding is not adequately understood. Consequently, there is no recommendation to treat maternal hyperthyroidism with the aim of enhancing lactation at this moment (No recommendation, insufficient evidence). • The use of131I is not recommended during breastfeeding. If necessary, 123I can be utilized provided that breast milk is expressed and disposed of for 3–4 days before breastfeeding is resumed. Similarly, if Tc-99m pertechnetate is administered, it is necessary to pump and discard breast milk during the day of the testing procedure (Strong recommendation, moderate-quality evidence). • The decision to treat hyperthyroidism in lactating women should be guided by the same principles

			applied to non-lactating women (Strong recommendation, low-quality evidence). • When antithyroid medication is necessary for women who are breastfeeding, both MMI (up to a maximum dose of 20 mg/day) and PTU (up to a maximum dose of 450 mg/day) can be used. Since a small but measurable amount of both PTU and MMI can pass into breast milk, it is recommended to use the lowest effective dose of MMI/Carbimazole or PTU (Strong recommendation, moderate-quality evidence). • Breastfed infants born to mothers receiving ATD treatment should undergo regular pediatric health check-ups to ensure proper growth and development. It is not necessary to routinely test the child's thyroid function (Weak recommendation, moderate-quality evidence) • All patients with depression, including postpartum depression, should be screened for thyroid dysfunction (Strong recommendation, low-quality evidence). • In the hyperthyroid phase of postpartum thyroiditis (PPT), symptomatic women can receive treatment with beta-blockers. A safe beta-blocker for lactating women, like propranolol or metoprolol, should be used at the lowest effective dose to relieve symptoms. This treatment is generally necessary for a few weeks (Strong recommendation, moderate-quality evidence). • ATDs are not recommended for the treatment of the thyrotoxic phase of PPT (Strong recommendation, high-quality evidence)

			• Following the resolution of the thyrotoxic phase of PPT, serum TSH should be measured in approximately 4–8weeks (or if new symptoms develop) to screen for the hypothyroid phase (Strong recommendation, high-quality evidence). • There is not enough evidence to support or oppose the idea of screening all pregnant women for abnormal TSH levels in the early stages of pregnancy (No recommendation, insufficient evidence). • There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations preconception, with the exception of women planning assisted reproduction or those known to have TPOAb positivity (No recommendation, insufficient evidence). • All pregnant women should be verbally screened at the initial prenatal visit for any history of thyroid dysfunction, and prior or current use of either thyroid hormone (LT4) or antithyroid medications (MMI, CM, or PTU) (Strong recommendation, high-quality evidence).
		The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of	• Evaluate GO according to standardized criteria, categorizing it as active or inactive, and mild, moderate-to-severe, or sight-threatening. Include the assessment of quality of life using the GO-QoL questionnaire (1, ØØØO). • Primary-care physicians, general practitioners, general internists, and specialists should refer patients with overt GO and mild cases at risk of deterioration (such as clinically active GO, smokers, severe/unstable

		Graves' orbitopathy[9]	hyperthyroidism, high serum TSHR-Ab titers) to combined thyroid-eye clinics or specialized centers with expertise in both endocrinology and ophthalmology. This will lead to accurate diagnosis and improved prognosis and quality of life (1, ØØOO). • Physicians should advise all patients with Graves' hyperthyroidism, regardless of the presence of GO, to quit smoking (1, ØØØØ). • Restore and maintain euthyroidism promptly in all patients with GO (1, ØØØØ). • Provide oral prednisone/prednisolone prophylaxis to RAI-treated patients at risk of GO progression or development (e.g., smokers, severe/unstable hyperthyroidism, high serum TSHR-Ab). Regimen depends on risk level. Patients with longstanding and stably inactive GO can receive RAI without prednisone/prednisolone cover if risk factors for GO progression are absent. Avoid uncontrolled post-RAI hypothyroidism (1, ØØØØ). • All GO patients should receive extensive local treatment with artificial tears throughout the disease course unless corneal exposure necessitates higher protection, especially at nighttime (1, ØØOO). • Mild GO should be managed with local treatments and general measures to control risk factors. Patients with mild and active GO of recent onset should receive a 6-month selenium supplementation, as it improves eye manifestations and quality of life and usually prevents GO progression (1, ØØØO).

			• If the impact of the disease on quality of life outweighs the risks, low-dose immunomodulatory therapy (for active GO) or rehabilitative surgery (for inactive GO) can be considered after thorough counseling and shared decision-making (2, ØØOO). • Provide extensive counseling to inform patients about the aims, expectations, benefits, and risks of different therapies. The selection of treatment should consider evidence-based effectiveness, safety, costs, health system reimbursement, drug availability, treatment facilities, and the patient's informed choice within a shared decision-making process (1, ØØOO). • Limit the cumulative dose of i.v. glucocorticoids to a maximum of 8.0 g per cycle. Patients with recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity, or uncontrolled hypertension should not receive i.v. glucocorticoids. Ensure well-controlled diabetes before starting treatment and administer this treatment only in experienced centers capable of managing potential serious adverse events (1, ØØØO) • In most cases of moderate-to-severe and active GO, an intermediate dose of intravenous glucocorticoids is recommended. This includes a starting dose of 0.5 g of intravenous methylprednisolone once weekly for 6 weeks, followed by 0.25 g once weekly for 6 weeks, resulting in a cumulative dose of 4.5 g (1, ØØØØ). • A high-dose regimen of intravenous glucocorticoids is reserved for more severe cases within the moderate-

			to-severe and active GO spectrum. This regimen involves a starting dose of 0.75 g of intravenous methylprednisolone once weekly for 6 weeks, followed by 0.5 g once weekly for 6 weeks, resulting in a cumulative dose of 7.5 g (1, ØØØO). • Clinicians should closely monitor individual patients receiving glucocorticoid therapy for treatment response and adverse events. If the side effects of glucocorticoid treatment outweigh the benefits, clinicians should consider discontinuing glucocorticoid therapy in favor of an alternative approach or vigilant monitoring (2, ØØOO). • Local subconjunctival/periocular injections of triamcinolone acetate may be considered when systemic glucocorticoids are absolutely contraindicated (2, ØØOO). • Mycophenolate demonstrates a favorable efficacy/safety profile in patients with moderate-to-severe and active GO, either as monotherapy or in combination with intravenous glucocorticoids (1, ØØØØ). • Orbital radiotherapy is considered an effective second-line treatment for moderate-to-severe and active GO, especially when combined with glucocorticoids, particularly in the presence of diplopia and/or restriction of extraocular motility (1, ØØØO). • The combination of cyclosporine and oral glucocorticoids is a valid second-line treatment for moderate-to-severe and active GO (1, ØØØØ).

			• Consideration may be given to azathioprine as a second-line and glucocorticoid-sparing agent in combination with oral glucocorticoids (1, ØØOO). • Teprotumumab is a very promising drug with a strong reduction in exophthalmos, diplopia, and improvement in quality of life. It is currently considered a second-line option, pending longer-term data, availability, affordability, costs, and the need for subsequent rehabilitative surgery (1, ØØØO). • Rituximab can be considered a second-line treatment for patients with moderate-to-severe and active GO of recent onset (<12 months) if refractory to intravenous glucocorticoids, with the exclusion of dysthyroid optic neuropathy (DON). This treatment should be administered in experienced centers capable of managing potentially serious adverse events (1, ØØOO). • The first-line treatment for moderate-to-severe and active GO consists of intravenous methylprednisolone in combination with oral mycophenolate sodium (or mofetil) (1, ØØØO). • In more severe forms of moderate-to-severe and active GO, including constant/inconstant diplopia, severe inflammatory signs, and exophthalmos > 25 mm, intravenous methylprednisolone at the highest cumulative dose (7.5 g per cycle) as monotherapy represents an additional valid first-line treatment (1, ØØØO)

			• If the response to primary treatment is inadequate, and GO remains at a moderate-to-severe and active stage, considering the following second-line treatments is recommended: I. A second course of intravenous methylprednisolone monotherapy, commencing with high single doses (0.75 g) and a maximum cumulative dose of 8 g per cycle. II. Combining oral prednisone/prednisolone with either cyclosporine or azathioprine. III. Employing orbital radiotherapy in conjunction with oral or intravenous glucocorticoids. IV. Considering the use of Teprotumumab, Rituximab, or Tocilizumab (1, ØØØO). • Although based solely on expert opinion due to the lack of randomized trials, the task force suggests that combining orbital radiotherapy with intravenous methylprednisolone is a potential second-line treatment for moderate-to-severe and active GO (2, ØØOO). • In cases of optic neuropathy, immediate treatment with high single doses of intravenous methylprednisolone (0.5–1 g of methylprednisolone daily for three consecutive days or preferably on alternate days) is advised. If there is an inadequate or absent response within 1–2 weeks, urgent orbital decompression should be performed. Recent eyeball subluxation should also undergo orbital decompression as soon as possible. Severe corneal

			exposure necessitates urgent medical treatment or progressively more invasive surgeries to prevent corneal breakdown, with immediate surgical intervention required in cases of corneal breakdown (1, ØØØO for optic neuropathy, and 2, ØØOO for corneal exposure). • For patients with mild and inactive GO, any treatment for hyperthyroidism can be utilized based on standardized criteria and patient preference (1, ØØOO). • In cases of mild and active GO, the preferred options are antithyroid drugs (ATDs) or thyroidectomy. If radioactive iodine (RAI) treatment is chosen, prophylaxis with prednisone/prednisolone should be considered (1, ØØØO). • Similar to mild and inactive GO, thyroid treatment can follow standardized criteria and patient choice. However, in cases where RAI treatment is selected, consideration should be given to prednisone/prednisolone prophylaxis if risk factors (e.g., smoking, high TSHR-Ab) are present (1, ØØOO). • In cases of moderate-to-severe and active GO, the primary focus should be on treating hyperthyroidism with ATDs until the treatment of GO is completed (1, ØØØO). • In emergencies involving sight-threatening GO, the absolute priority is to treat GO. Hyperthyroidism should also be managed with ATDs until the treatment of GO is concluded (1, ØØØO).

	Missing	2016 Guidelines for the management of thyroid storm from The Japan Thyroid Association and Japan Endocrine Society (First edition)[11]	• Thyroid storm is an urgent endocrine situation characterized by rapid deterioration occurring within days or even hours after initial presentation and is associated with a high mortality rate. While most instances of thyroid storm arise due to the presence of a precipitating factor in combination with an underlying thyroid condition, typically untreated or poorly managed Graves' disease, exceptionally rare cases can involve other hyperthyroid conditions such as destructive thyroiditis, toxic multinodular goiter, TSH-secreting pituitary adenoma, hCG-secreting hydatidiform mole, or metastatic thyroid cancer. • To mitigate the effects of thyrotoxicosis on various organ systems, a multifaceted strategy involving antithyroid drugs (ATDs), inorganic iodide, corticosteroids, beta-adrenergic antagonists (beta-AAs), and antipyretic agents (Strength of recommendation: high, Quality of evidence: moderate) • ATDs, either MMI or PTU, should be administered for the treatment of hyperthyroidism in thyroid storm (Strength of recommendation: high, Quality of evidence: low) • Intravenous administration of MMI is recommended in severely ill patients with consciousness disturbances or impaired gastrointestinal tract function. (Strength of recommendation: high, Quality of evidence: low) • In cases of thyroid storm resulting from hyperthyroid conditions, inorganic iodide should be administered in

			conjunction with antithyroid drugs (ATDs) (Strength of recommendation: high, Quality of evidence: moderate) • Corticosteroids (300 mg/day hydrocortisone or 8 mg/day dexamethasone) should be administered to patients with thyroid storm regardless of its origin) Strength of recommendation: high, Quality of evidence: moderate) • For individuals experiencing thyroid storm with elevated body temperature, proactive cooling should be initiated using acetaminophen along with physical cooling methods such as cooling blankets or ice packs (Strength of recommendation: high, Quality of evidence: moderate) • Therapeutic plasmapheresis (TPE) may be contemplated if there is no observable clinical improvement within 24 to 48 hours following the initial treatment, which should include adequate doses of antithyroid drugs, inorganic iodine, corticosteroids, or beta-adrenergic antagonists, in addition to specific treatment for the underlying condition and complications associated with thyroid storm) Strength of recommendation: weak, Quality of evidence: low) • Apart from promptly addressing thyrotoxicosis, it is essential to differentially diagnose and treat acute consciousness disturbances, psychosis, and seizures in cases of thyroid storm. This should be carried out following established guidelines and in consultation with a psychiatrist or neurologist (Strength of recommendation: strong, Quality of evidence: low)

			• The preferred initial treatment for tachycardia in thyroid storm should be beta1-selective adrenergic antagonists (AAs) like landiolol, esmolol (administered intravenously), or bisoprolol (given orally). Other oral medications with beta1-selective activity are also considered suitable. While non-selective beta-AAs like propranolol are not contraindicated, they are not recommended for managing tachycardia in thyroid storm. 6. In patients classified as Killip class ≤ III, if their heart rate is ≥150 bpm, the initial treatment choice should be either landiolol or esmolol. When the heart rate falls below 150 bpm, it's possible to switch to an oral beta1-selective medication. 7. For patients in Killip class IV, the use of landiolol or esmolol may be considered if their heart rate is ≥150 bpm. 8. Landiolol should be initiated intravenously at a dose of 1 μg/kg/min, with appropriate dosage adjustments while monitoring the heart rate (in the range of 1–10 μg/kg/min). Esmolol should be started intravenously with a 1 mg/kg dose over 30 seconds, and its dosage should be adjusted as needed while monitoring the heart rate (approximately ~150 μg/kg/min). Bisoprolol is administered orally at a daily dose of 2.5–5 mg. 9. The heart rate should be controlled to ≤130 bpm when using beta-Adrenergic Antagonists (beta-AAs). Consider discontinuing beta-AAs if the heart rate falls

			below 80 bpm, systolic blood pressure is less than 80 mmHg, or the cardiac index is ≤2.2 L/min/m2. 10. Exercise caution when using landiolol or esmolol in patients with bronchial asthma and chronic obstructive pulmonary disease (COPD). Consider switching to verapamil or diltiazem if an asthma attack occurs (Strength of recommendation: high, Quality of evidence: low) • When atrial fibrillation occurs: 4. Digitalis is used in patients without severe renal dysfunction. It is given intravenously at an initial dose of 0.125 to 0.25 mg, followed by an appropriate maintenance dose with careful monitoring for signs and symptoms of digitalis toxicity. 5. When there is a rapid deterioration of hemodynamics due to atrial fibrillation, it is advisable to perform cardioversion after ruling out the presence of left atrial thrombus. 6. Class Ia and Ic antiarrhythmic drugs are suggested for the maintenance of sinus rhythm following cardioversion. In cases where there is impaired left ventricular systolic function, amiodarone might be considered as a treatment option (Strength of recommendation: high, Quality of evidence: low) • For persistent atrial fibrillation, the decision to use anticoagulation should be based on the CHADS2 score, which is a tool used to assess the risk of stroke occurrence (Strength of recommendation: high, Quality of evidence: low)

			• Patients with acute congestive heart failure classified as Killip class ≥III should undergo hemodynamic monitoring using a Swan-Ganz catheter, as recommended (Strength of recommendation: high, Quality of evidence: low) • Acute congestive heart failure in thyroid storm should be treated according to the Guidelines for the Treatment of Acute Heart Failure (JCS 2011), given the pathophysiology of thyroid storm (Strength of recommendation: high, Quality of evidence: low) • In cases where the hemodynamic status has not improved with the maximum dose of adrenergic agonists and there is a risk of irreversible multiple organ failure, it is advisable to employ an artificial heart-lung machine as a therapeutic measure (Strength of recommendation: high, Quality of evidence: low) • Gastrointestinal symptoms like diarrhea, nausea, and vomiting are linked to conditions such as thyrotoxicosis, heart failure, neurological disorders, and gastrointestinal infections. When treating gastrointestinal infections in parallel with thyrotoxicosis, it can help alleviate these symptoms (Strength of recommendation: strong, Quality of evidence: low) • The administration of high doses of corticosteroids, the presence of coagulopathy related to thyroid storm, and prolonged stays in the intensive care unit with extended mechanical ventilation may increase the risk

			of gastrointestinal bleeding and mortality. To mitigate these risks, acid-suppressive medications like proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2As) are recommended for patients in these situations (Strength of recommendation: strong, Quality of evidence: low) • Hepatotoxicity, with or without jaundice, in thyroid storm can result from various factors, including hepatocyte damage due to thyrotoxicosis, heart failure, hepatic-biliary infection, or drug-induced liver injury. Surveys conducted nationwide have shown that a worse prognosis is associated with total bilirubin levels equal to or greater than 3.0 mg/dL. To address hepatic dysfunction, a thorough differential diagnosis of its origin should be performed, and treatment tailored to the underlying cause, including therapeutic plasmapheresis (TPE) for acute hepatic failure, should be considered (Strength of recommendation: strong, Quality of evidence: low) • Intensive care unit (ICU) admission should be recommended for all thyroid storm patients. Patients with potentially fatal conditions such as shock, DIC, and multiple organ failure should immediately be admitted to the ICU. (Strength of recommendation: strong, Quality of evidence: low) • The APACHE II score or Sequential Organ Failure Assessment score can be used for the prognostic prediction of thyroid storm. (Strength of recommendation: weak, Quality of evidence: low)

			• It is crucial to take preventive measures to avoid thyroid storm in patients with poor adherence who are receiving antithyroid drug (ATD) treatment (Strength of recommendation: high, Quality of evidence: low) • To prevent the recurrence of thyroid storm in patients who have been effectively managed during the acute phase of thyroid storm, consideration should be given to definitive treatments for Graves' disease, such as radioiodine treatment or thyroidectomy (Strength of recommendation: high, Quality of evidence: low) • When patients exhibit elevated body temperature (≥38°C), significant tachycardia (≥130 beats per minute), and symptoms originating from various organ systems such as the central nervous system, cardiovascular system, and gastrointestinal tract, it is crucial to consider the potential occurrence of thyroid storm. When there is suspicion of thyroid storm, healthcare providers should refer to the diagnostic criteria established for thyroid storm [4, 8]. This reference should be made during the initial assessment, which follows the ABCDE (Airway, Breathing, Circulation, Dysfunction of the Central Nervous System, Exposure & Environmental Control) approach to evaluation and treatment. Patients who raise a high suspicion of having thyroid storm based on these criteria should be promptly transferred to a general hospital equipped with an intensive care unit (ICU) and staffed with specialists in endocrinology and other relevant subspecialties (Strength of recommendation: high, Quality of evidence: low).

Appendix C. MeSH Terms PubMed

C.1 Pubmed Search for Hyperthyroidism

The following is the result of the PubMed search conducted for hyperthyroidism guideline search:

Query	Filters	Search Details	Results
((((Hyperthyroidism[MeSH Terms]) OR (Hyperthyroid[Title/Abstract])) OR (Hyperthyroids[Title/Abstract])) OR (Primary Hyperthyroidism[Title/Abstract])) OR (Hyperthyroidism, Primary[Title/Abstract])	Guideline, in the last 5 years	("Hyperthyroidism"[MeSH Terms] OR "Hyperthyroid"[Title/Abstract] OR "Hyperthyroids"[Title/Abstract] OR "primary hyperthyroidism"[Title/Abstract] OR "hyperthyroidism primary"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	16

Appendix D. Treatment Algorithm

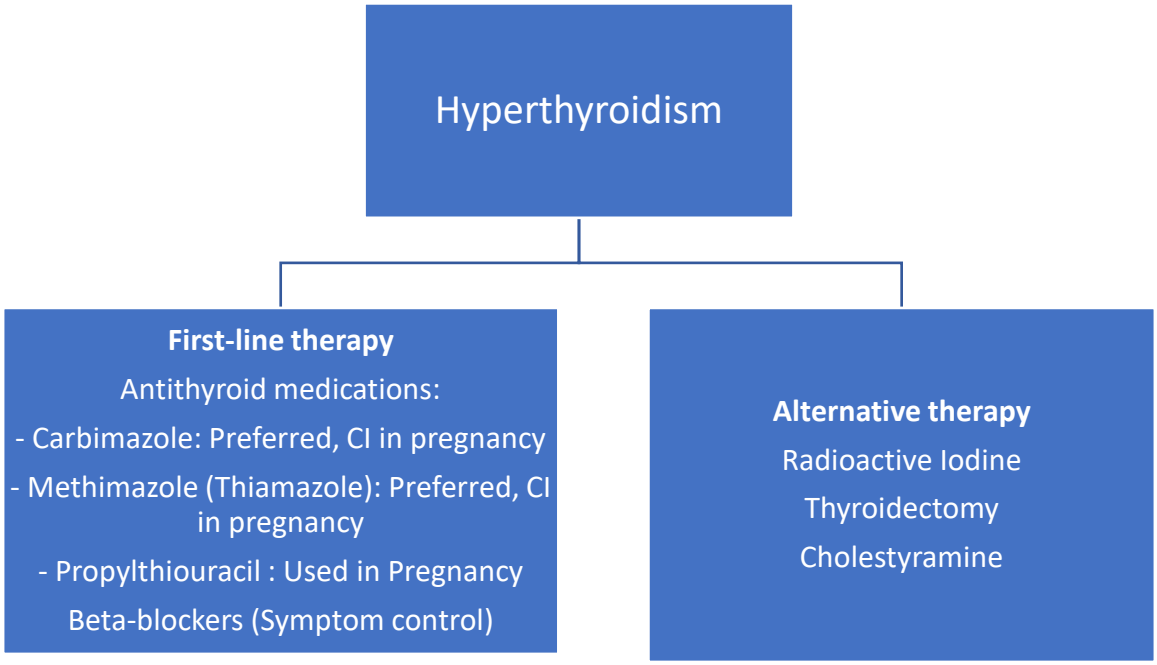

Figure 7. *Treatment Algorithm of Hyperthyroidism*[5,6,10,21]