Thyroid Disorders

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Abbreviations

AF	atrial fibrillation	NAFLD	non-alcoholic fatty liver disease
AITD	autoimmune thyroid diseases	NSAIDs	non-steroidal anti-inflammatory drugs
ART	assisted reproductive technology	OH	overt hypothyroidism
ATD	anti-thyroid drugs	PR	pregnancy-specific reference range
BB	beta blocker	PTU	propylthiouracil
BMD	bone mineral density	QoL	quality of life
CCB	calcium channel blocker	RAI	radioactive iodine
CHD	coronary heart disease	SERM	Selective oestrogen receptor modulator
CVD	cardiovascular disease	SH	subclinical hypothyroidism
DXA	dual-energy X-ray absorptiometry	STN	solitary thyroid nodule
FSH	follicular stimulating hormone	TA	toxic adenoma
FT3	free triiodothyronine	TBG	thyroxine binding globulin
FT4	free thyroxine	TFT	thyroid function tests
G-CSF	granulocyte colony stimulating factor	TH	thyroid hormone
GAG	glycosaminoglycans	TIRADS	Thyroid Imaging Reporting and Data System
GC	glucocorticoids	TPO	thyroid peroxidase
GD	Graves disease	TRAb	TSH receptor antibodies
GO	Graves orbitopathy	TRH	thyrotropin-releasing hormone
hCG	human chorionic gonadotrophin	TSH	thyroid stimulating hormone
HPT	hypothalamo-pituitary thyroid axis	TSHR	TSH receptor
LFT	liver function tests	TT3	total triiodothyronine
LH	luteinizing hormone	TT4	total thyroxine
LT4	levothyroxine	TTR	transthyretin
LDL	low density lipoprotein	ULN	upper limit of normal
MNG	multi-nodular goitre		

1. INTRODUCTION

Thyroid hormones (TH) play a vital role in the normal growth and metabolism. Thyroid disorders can have a significant impact on wellbeing and quality of life (QoL) of individuals and on the healthcare system of the country. Therefore, evidence based, up to date guidelines on investigation and management of these disorders, adapted to the local setting are a timely requirement.

Thyroid disorders can present with hypofunction or hyperfunction of the gland, as well as benign or malignant thyroid nodules. Focus of this clinical practice guideline is on hypothyroidism and thyrotoxicosis.

1.1. Epidemiology

Global situation

Global distribution of thyroid disorders varies based on several factors, including gender, iodine status, predisposition to autoimmunity, smoking, alcohol consumption and genetic factors. Overall, thyroid disorders are more common among females. Nodular thyroid disorders are more frequently found in iodine deficient areas, while autoimmune thyroid disorders are common in iodine replete areas (1).

Hypothyroidism

Iodine deficiency and thyroid autoimmunity (Hashimoto thyroiditis) are the commonest causes for hypothyroidism. In iodine sufficient areas, prevalence of overt hypothyroidism is 1-2% and is 10 times commoner among females than males, with an increasing prevalence with age (2). Worldwide annual incidence of Hashimoto thyroiditis is estimated to be 0.3-1.5 cases per 1000 persons (2)(3).

Hyperthyroidism

Overall prevalence of hyperthyroidism is estimated to be 1.3% and incidence is 2.7% in females and 0.7% in males (4)(5). Graves disease (GD) is the most common cause for hyperthyroidism, followed by toxic multi-nodular goitre (MNG) (4). GD contributes to 70-80% of all cases of hyperthyroidism in iodine sufficient countries while in iodine deficient countries it contributes to 50% of all cases (6)(7). Toxic MNG and solitary toxic nodule (STN) are more prevalent in iodine deficient areas.

Thyroid dysfunction in pregnancy

The prevalence of overt hypothyroidism, subclinical hypothyroidism and isolated hypothyroxinaemia during pregnancy is 0.5%, 3.5% and 2.1% respectively in the west (8). Estimated incidence of overt thyrotoxicosis in pregnancy is 0.2% and subclinical thyrotoxicosis is 2.5% (8). GD is the most common cause for thyrotoxicosis in pregnancy.

Sri Lankan situation

Prior to 1995, high prevalence of iodine deficiency in Sri Lanka made the country endemic for goitres. Universal iodization of salt (initiated in 1995) was successful in overcoming this situation, resulting in a reduction of goitre prevalence in Sri Lanka from 18.2% in 1986 to 3.8% in 2005. The prevalence of autoimmune thyroid diseases (AITDs) was found to be between 16-20% (9). In a regional study done in 2014, thyroid dysfunction was present in 21.1% of patients with type 2 diabetes (subclinical hypothyroidism: 9.4%, overt hypothyroidism: 6.1%) (10).

1.2. Thyroid physiology

Regulation of TH production and secretion

TH biosynthesis [Figure 1.1.(a)] and secretion are under tight control of hypothalamo-pituitary-thyroid (HPT) axis [Figure 1.1.(b)].

Transport of THs in blood

THs circulate mainly in the bound form (more than 99.95% of T4 and 99.5% of T3) (Table 1.1). Alterations in serum levels of these proteins, mainly TBG can alter serum total T4 and T3 (TT4 and TT3) concentrations, without an effect on free hormone (FT4 and FT3) concentrations (11) (Table 1.2).

Action of THs

Actions of THs are mediated by binding to α and β T3 nuclear receptors, exerting genomic effects. These hormonal actions are important for brain and somatic development in neonates, metabolic functions, bone development and cardiac function in adults.

Thyroid function tests (TFT)

Thyroid functions are assessed by following tests (Table 1.3)

(a)

(b)

Figure 1.1.

(a) TH biosynthesis. Thyroxine (T₄) and 3,5,3' – triiodothyronine (T₃) are the 2 biologically active thyroid hormones. Iodine is essential for thyroid hormone synthesis. T₄ is produced at a rate of 80-100 µg per day by the thyroid. T₃ is mainly produced by extra-thyroidal deiodination (80%)

(b) Regulation of TH Red arrows: inhibitory signal, green arrows: stimulatory signal. TRH: thyrotropin releasing hormone, TSH: thyroid stimulating hormone, T₃: tri-iodothyronine, T₄: tetra-iodothyronine (thyroxine) Note: TSH has 2 subunits; α and β. α-subunit is similar to LH, FSH and hCG and β-subunit is unique to TSH

Table 1.1. Transport of TH and binding proteins

Type of protein	Percentage of T4 bound	Percentage of T3 bound
Thyroxine binding globulin (TBG)	75%	80%
Transthyretin (TTR)	10%	5%
Albumin	12%	15%

Table 1.2. Factors altering TBG levels and TH binding

Elevated TBG	Suppressed TBG	Factors inhibiting the binding to proteins
Pregnancy	Androgens	Salicylates
High oestrogen level	Anabolic steroids	Fruzemide
Hepatitis	Glucocorticoids	Phenytoin
Porphyria	Severe illness	Carbamazepine
Heroin	Liver failure	NSAIDs
Methadone	Nicotinic acid	Heparin
Mitotane		
5 - fluorouracil		
Selective oestrogen receptor modulators (SERMs)		

Table 1.3. Considerations for interpretation of thyroid functions

Test	Considerations
TSH	<p>Upper limit of the normal range of TSH increases with age.</p> <p>TSH secretion follows a circadian rhythm, with highest levels in early morning, and lowest in late afternoon, causing only slight variations of TSH by 0.95 mIU/ml to 2 mIU/ml and does not necessarily reflect a change in thyroid status (12)(13).</p> <p>Assay interferences can occur with the heterophile antibodies leading to either falsely elevated or suppressed TSH values. E.g.: Graves disease, sero-positive rheumatoid arthritis (13).</p> <p>TSH level correlates positively with body mass index (BMI). Morbid obesity is associated with high TSH levels (14).</p> <p>Biotin can cause falsely low TSH values. Stop 2 days before the assay.</p>
TT4 , TT3	Affected by TBG level and its binding to T4 and T3 (Table 1.2)
FT4 , FT3	<p>Measures unbound fraction and therefore is unaffected by alterations of binding to proteins.</p> <p>Biotin can cause falsely high values in FT4 and FT3 measurements. Stop biotin for 2 days prior to the test (15).</p>

2. HYPOTHYROIDISM

2.1. Introduction

Hypothyroidism is a syndrome that results from abnormally low secretion of THs from the thyroid gland, leading to a decrease in basal metabolic rate and multisystem dysfunction. The most severe form is known as myxoedema.

2.2 Causes of hypothyroidism

Hypothyroidism may be primary, secondary or tertiary due to thyroid disease, pituitary disease, or hypothalamic dysfunction respectively. Primary hypothyroidism can be overt or subclinical (table 2.1)

Table 2.1. Classification of primary hypothyroidism

Overt hypothyroidism (OH)	Elevated TSH with sub-normal FT4
Subclinical hypothyroidism (SH)	TSH above the upper reference limit and a normal FT4
Note: This is only applicable when thyroid function has been stable for 3 months or more, the hypothalamo-pituitary function is normal, and there is no recent or on-going severe illness	

2.2.1. Causes of primary hypothyroidism

These causes are summarised in table 2.2

Table 2.2. Causes of primary hypothyroidism

Congenital	Thyroid agenesis / dysplasia Defects in thyroid hormone synthesis
Acquired	Chronic autoimmune thyroiditis / Hashimoto's thyroiditis Post-thyroidectomy Iodine deficiency Post radio-iodine thyroid ablation External beam radiotherapy for non-thyroidal head and neck malignancy Drugs inhibiting the synthesis or release of thyroxine – Lithium, iodide, over treatment of hyperthyroidism Infiltrative diseases – e.g.: sarcoidosis

Autoimmune thyroid diseases (AITDs)

- Auto-immunity against the thyroid leads to two distinct pathogenic processes with opposing clinical outcomes: hypothyroidism in Hashimoto's thyroiditis and hyperthyroidism in GD (except when TSH receptor antibodies have inhibitory effects, where hypothyroidism results)
- Pathogenesis and risk factors of AITD are illustrated in Figure 2.1 and 2.2 respectively.
- Many patients with autoimmune thyroid disease are biochemically euthyroid, but 75% of them harbour circulating anti-thyroid antibodies, the presence of which predicts progression to hypothyroidism (16).

Figure 2.1. Pathogenesis of Hashimoto's thyroiditis (17).
Dysregulation of humoral and cell mediated immune responses leads to destruction of thyroid cells over time.
Presence of circulating antibodies predicts progression to overt hypothyroidism

2.2.2. Central hypothyroidism (Secondary and tertiary hypothyroidism)

Hypothalamic or pituitary diseases result in central hypothyroidism. In this condition TSH level may be low or inappropriately normal for the level of FT4 and therefore not a useful monitoring marker when thyroxine

replacement is started. FT4 levels should be maintained within the upper half of the reference range when treating central hypothyroidism.

2.3. Diseases associated with hypothyroidism

Several autoimmune diseases and genetic / congenital syndromes are associated with hypothyroidism (table 2.3).

Figure 2.2. Risk factors for Hashimoto's thyroiditis (2), (5), (18), (19), (20), (21), and (22)

Table 2.3. Diseases and syndromes associated with hypothyroidism (18)

Associated autoimmune diseases	Other associated syndromes
Vitiligo	Pendred syndrome
Addison disease	Down syndrome
Type 1 diabetes mellitus	Turner syndrome
Rheumatoid arthritis	Bamforth-Lazarus syndrome
Chronic autoimmune gastritis	Brain-lung-thyroid syndrome
Pernicious anaemia	
Systemic lupus erythematosus	
Ulcerative colitis	
Multiple sclerosis	
Psoriatic arthritis	
Myasthenia gravis	
Coeliac disease

Figure 2.3. Symptoms and signs of hypothyroidism (19)

2.4. Clinical features of hypothyroidism

The symptoms and signs of hypothyroidism (figure 2.3) depend on the severity of TH deficiency and the rapidity at which it occurs. Associated hypogonadism and adrenal insufficiency in central hypothyroidism may mask the manifestations of hypothyroidism.

2.5. Evaluation of hypothyroidism

Evaluation for hypothyroidism should be done in all patients presenting with clinical features of hypothyroidism or in special situations which are mentioned in box 2.1 (20)(21).

2.5.1. Diagnosis of hypothyroidism

Due to the lack of specificity of the clinical manifestations, the diagnosis of hypothyroidism is based primarily upon TFTs which include TSH and FT4.

It is recommended to use local laboratory reference range when interpreting TFTs.

Note: If an abnormal thyroid function report is not compatible with the clinical presentation, the test should be repeated.

Elevated TSH and normal FT4 should be demonstrated on at least 2 occasions, 3 months apart to diagnose subclinical hypothyroidism.

2.5.2 .Supportive tests for evaluation of hypothyroidism

Supportive tests (Table 2.4) are used to identify the aetiology and complications of hypothyroidism.

Box 2.1. Special situations to suspect hypothyroidism

1. Personal risk factors
 - Strong family history of hypothyroidism
 - Newborns of mothers with thyroid diseases (In Sri Lanka all the newborn babies are screened with heel prick TSH test)
 - Past history of neck irradiation, RAI, thyroid surgery
 - Patients on drugs such as lithium, amiodarone
 - Patients with other autoimmune diseases
2. Patients with a goitre
3. Associated syndromes - Turner syndrome, Down syndrome (table 2.3)
4. Abnormal biochemistry
 - Substantial hyperlipidaemia
 - Unexplained hyponatraemia
 - High serum creatine kinase
 - Macrocytic anaemia
5. Associated clinical conditions
 - Pericardial or pleural effusions
 - Pituitary or hypothalamic disorders

Figure 2.4. Diagnosis of hypothyroidism

Table 2.4. Supportive tests for evaluation of hypothyroidism

Supportive tests	Expected results
Ultrasound scan of thyroid	<ul style="list-style-type: none"> To evaluate the goitre if present Look for nodularity / diffuse enlargement If nodule present, determine the TIRADS score for risk stratification
Thyroid peroxidase (TPO) antibodies	Elevated in over 90% of patients with autoimmune thyroiditis, the most common cause of primary hypothyroidism.

TIRADS: Thyroid Imaging Reporting and Data System – a scoring system to stratify risk of malignancy based on ultrasound appearance

2.6. Management of hypothyroidism

All the patients diagnosed with overt hypothyroidism will require levothyroxine (LT4) replacement.

2.6.1. Initiation of levothyroxine replacement

- LT4 is the mainstay of treatment since biologically active T3 is generated by the peripheral conversion of LT4 (20).
- The dose can range from 50 to ≥ 200 $\mu\text{g/day}$ (see table for exceptions). Lower doses (e.g. 25–50 $\mu\text{g/day}$) will be required in milder degrees of hypothyroidism; for example, if the serum TSH is <10 mIU/L or if the patient has subclinical hypothyroidism.
- Starting dose of levothyroxine is decided based on individual characteristics of the patient (20).

The usual starting dose of LT4 is 1.6–1.8 $\mu\text{g/kg/day}$ of actual body weight rounded to the nearest 25 μg (20).

Table 2.5. Individual patient characteristics determining the starting levothyroxine dose

Factor	Considerations
Body weight	<ul style="list-style-type: none"> The ideal body weight is a better predictor of LT4 dose than the actual body weight (22).
Pregnancy status	<ul style="list-style-type: none"> Women being treated for hypothyroidism typically require an increase in their LT4 dose when pregnant.
Aetiology of hypothyroidism	<ul style="list-style-type: none"> Patients who have undergone thyroidectomy generally require a higher LT4 dose than patients with Hashimoto's thyroiditis. Patients who have received radioiodine therapy (RAI) for GD may have a variable need for LT4, depending on the residual functional thyroid tissue.
Age	<ul style="list-style-type: none"> LT4 dose requirement tends to decrease with age despite the decrease in LT4 absorption with advancing age (23).
General clinical context	<ul style="list-style-type: none"> Presence of cardiac disease: LT4 therapy may exacerbate angina in patients with ischaemic heart disease. It is recommended to start with a lower dose of LT4 (12.5–25 µg/day) with titration in small increments every 6 weeks to a full therapeutic dose while paying close attention to the development of ischaemic symptoms
Differentiated thyroid cancer	<ul style="list-style-type: none"> LT4 dose requirement in patients with differentiated thyroid cancer requiring TSH suppression after thyroidectomy are generally higher and usually between 2.1–2.7 µg/kg (24).

2.6.2.. Administration of levothyroxine

Box 2.2. Administration of levothyroxine

- LT4 should be taken either 60 minutes before breakfast (or in selected patients, at bedtime - 3 or more hours after the evening meal) as co-ingestion of food is likely to impair the absorption
- LT4 intake should be separated from other potentially interfering medications and supplements by 4 hours
- LT4 should be stored at a temperature of less than 25° C
- Store in the original package in order to protect from light and moisture

2.6.3. Monitoring of levothyroxine treatment

Box 2.3. Monitoring of levothyroxine treatment (20)(21)

Monitoring is done with serum TSH level

- Maintain TSH in the normal range (refer the local lab reference values)
- Check TSH in 4–6 weeks after the initiation or dose adjustment of LT4
- Once the TSH level is stable, patients can be monitored yearly
- Dose adjustments should be made when there are large changes in body weight, with ageing, co-treatment with drugs that alter thyroxine metabolism (e.g.: carbamazepine) and with pregnancy

Note: Monitoring is different in central hypothyroidism, peripheral thyroid hormone resistance, and in the presence analytic interference with its measurement. In central hypothyroidism, monitor FT4.

2.6.4. Treatment outcome

Symptomatic improvement is expected within 2 weeks. Optimum treatment with LT4 will also normalize the TSH level (16). Avoid overtreatment, especially in the elderly (20).

2.6.5. Over-treatment and under-treatment

All patients should be evaluated for clinical features of over/under treatment. Avoid subnormal serum TSH values, particularly values below 0.1 mIU/L, especially in older persons and postmenopausal women.

Table 2.6. Over and under-treatment with levothyroxine

Adverse effects of over treatment	Adverse effects of under-treatment
<ul style="list-style-type: none">Increased risk of osteoporosisAtrial fibrillation (25)	<ul style="list-style-type: none">DyslipidaemiaProgression of atherosclerotic cardiovascular diseaseProgression of congestive heart failureReversible cardiomyopathy

2.7. Management of subclinical hypothyroidism (SH)

Persistent elevation of TSH with normal FT4 (at least on 2 occasions 3 months apart) is required to establish the diagnosis and consider treatment.

2.7.1. Consequences of subclinical hypothyroidism

1. Progression to overt hypothyroidism (OH)

Annual rate of progression to OH ranges from 2-4% (26).

Higher TSH at presentation, presence of TPO antibodies and the underlying disease may predict progression.

Patients who have AITD or received RAI or high-dose therapeutic external radiotherapy are likely to progress to overt hypothyroidism (27).

2. Cardiovascular disease

SH may be associated with an increased risk of coronary heart disease (25), heart failure (28), stroke (29), elevated total and LDL cholesterol (30), particularly when the serum TSH concentration is above 10 mU/L.

3. Non-alcoholic fatty liver disease

Elevated TSH levels show a positive correlation with the presence of NAFLD (30).

The effects of treating SH on mortality and reproductive abnormalities are not well studied and available evidence show conflicting results.

2.7.2. Benefits of TH Replacement in SH

- Alleviation of hypothyroid signs and symptoms
- May lead to improvements in major adverse cardiovascular events, serum lipids and apolipoprotein concentrations (data limited)
- May improve fertility (data limited)

2.7.3. TH replacement in SH

Dosing considerations are summarized in table 2.7

Table 2.7. Levothyroxine replacement in subclinical hypothyroidism

TSH ≥ 10 mIU/L	Considering the high risk of progression to overt hypothyroidism and the increased risk of cardiovascular disease and its resultant higher mortality, treatment is recommended (21).
TSH 4.5-10 mIU/L	Routine treatment is not recommended. Treatment is decided by individual factors (e.g.: symptoms of hypothyroidism, positive TPO antibodies, subfertility or planning for pregnancy) (20).

2.7.4. Dosing and monitoring

Box 2.4. Dosing and monitoring of LT4 treatment in subclinical hypothyroidism

- Start with the lowest dose necessary to normalize the serum TSH concentration, typically 25 to 50 µg daily.
- Treatment goal is to normalize serum TSH.
- In patients who do not receive TH replacement, TFT should be repeated at regular intervals.
- In patients with TSH 4.5-10 mIU/L, if symptoms do not improve after starting LT4, re-measure TSH and if the level remains raised, adjust the dose. If symptoms persist while serum TSH is within the reference range, consider stopping LT4

2.8. Management of hypothyroidism in elderly

2.8.1. Physiological changes associated with ageing

With ageing multiple complex physiological changes occur in HPT axis and peripheral metabolism of TH. Upper limit of normal range for TSH increases progressively with ageing (figure 2.5) (31).

2.8.2. Guide for decision making

Diagnosis of overt and subclinical hypothyroidism is made using age specific reference ranges.

Clinical significance of diagnosis and benefits / potential risks of treatment of SH in elderly are a matter of debate (37) (38) (39).

Figure 2.5. Approximate changes in the serum TSH with ageing (31) (Reproduced with permission from Calsolaro V et al. Hypothyroidism in the Elderly: Who Should Be Treated and How? J Endocr Soc. 2019;3(1):146–58).

Treatment with LT4 should be considered in selected patients with higher TSH values or cardiovascular and cognitive dysfunction.

Symptoms attributable to hypothyroidism, frailty, burden of polypharmacy, patient preference and thyroid peroxidase antibody status may be considered in an individual basis to decide on treating SH (table 2.8) (31).

Use a smaller starting dose (25 µg/day or 0.4-0.5 µg/kg/day), since there is a possibility of worsening of subclinical CHD. Dose can be adjusted with clinical and biochemical monitoring (31)(32)(41).

Table 2.8. Suggested strategy to decide on treating subclinical hypothyroidism in elderly

Serum TSH value ^a (mIU/L)	Fit patient		Frail patient	
	65-75 years	>75 years	65-75 years	>75 years
>10	Treat	Treat ^b / Observe	Observe/ Treat ^b	Observe
6-10	Observe/ Treat ^{b,c}	Observe/ Treat ^{b,c}	Observe	Observe
4-6	Observe/ Treat ^{b,c}	Observe	Observe	Observe

a- Elevation of serum TSH value should be confirmed by at least a second measurement in 3-6 months
b- Consider treatment in the presence of positive TPO antibodies, symptoms of hypothyroidism, concomitant diseases potentially worsened by mild hypothyroidism (e.g.: heart failure), and patient's wish
c- Consider treatment if serum TSH value rises to ≥ 10 mIU/L

Treatment targets

Box 2.5. Treatment targets in elderly

In patients between 70-80 years, it is reasonable to keep a TSH target 4-6 mIU/L.
In patients above 80 years even slightly higher TSH reference values may be reasonable.
Iatrogenic subclinical hyperthyroidism should be avoided in these patients since it can be associated with increased cardiac complications and fractures (33)(34)(35).

Key recommendations: hypothyroidism

Diagnosis

Screen for hypothyroidism with TSH and FT4 if clinical features and / or biochemical derangements suggestive of hypothyroidism are present (box 2.1)

Diagnose primary or central hypothyroidism, and overt or subclinical hypothyroidism according to the pattern of TSH and FT4 (figure 2.4).

Treatment: overt hypothyroidism

Consider age, cardiovascular disease, pregnancy status, cause for hypothyroidism and body weight in determining the starting dose of LT4. Usual starting dose is 1.6 $\mu\text{g}/\text{kg}/\text{day}$ (table 2.5).

Advise patients to take levothyroxine in the morning, on empty stomach, and avoid other food or drinks (except water) for 60 minutes. Ensure other drugs interfering with absorption are spaced out (box 2.2).

Treatment: subclinical hypothyroidism

Consider treatment with LT4 if symptomatic, TSH is > 10 mIU/L, has TPO antibodies, has subfertility or is planning for pregnancy (table 2.7).

Start with a low LT4 dose and titrate (box 2.4)

Treatment of elderly

Consider progressive rise in TSH with ageing in healthy elderly before diagnosing hypothyroidism and deciding on treatment targets in elderly (figure 2.5).

Treat subclinical hypothyroidism in elderly with levothyroxine after considering age, frailty, degree of TSH elevation, TPO antibodies, symptoms and patient's wish (table 2.8).

Follow up

Reassess TSH in 4-6 weeks after treatment initiation. Aim for clinical euthyroidism and normalization of TSH in primary hypothyroidism and FT4 in central hypothyroidism (box 2.3). Once biochemically stable, reassessment of TSH can be done annually.

Refer to specialist

Consider referral to a specialist:

- If LT4 dose requirement is unusually high
- Patients with / suspected to have central hypothyroidism or thyroxine resistance
- Hypothyroidism in elderly or with concomitant cardiovascular disease

3. THYROTOXICOSIS

3.1. Introduction

Thyrotoxicosis is a clinical state resulting from inappropriately high circulating and tissue THs irrespective of the origin (36).

Hyperthyroidism is characterized by excessive synthesis and secretion of THs by the thyroid gland.

Thyrotoxicosis can be overt or subclinical depending on the biochemical profile.

Table 3.1. Classification of thyrotoxicosis

Overt thyrotoxicosis	Sub-clinical thyrotoxicosis
suppressed or undetectable levels of TSH increased FT4 and / or FT3	low TSH normal levels of FT4 and FT3

3.2. Causes of thyrotoxicosis

Causes can be broadly classified according to the presence or absence of hyperthyroidism. (Table 3.2)

Table 3.2. Causes of thyrotoxicosis

Thyrotoxicosis with hyperthyroidism	Thyrotoxicosis without hyperthyroidism
<ul style="list-style-type: none">Graves disease (GD)Toxic multinodular goitre (MNG)Toxic adenoma (TA) of thyroidTSH secreting pituitary adenomaPituitary resistance to thyroid hormonesTrophoblastic diseasesGestational thyrotoxicosis	<ul style="list-style-type: none">Subacute thyroiditis, painless thyroiditis: Inflammation and release of stores of thyroxine (viruses, drugs or toxins)Excess exogenous thyroid hormone - Iatrogenic or factitiousExposure to excess iodineEctopic thyroxine source : struma ovariiFunctional thyroid cancer metastasis

Graves disease

GD is an autoimmune disorder and is the leading cause of hyperthyroidism (37). About 3% of women and 0.1% of men develop GD during their lifetime (38).

TSH receptor antibodies (TRAb) targeted at thyrotropin receptor (TSHR) are central to the pathogenesis of GD (39). Several genes conferring increased susceptibility have been identified and these include genes encoding thyroglobulin, TSHR, HLA-DR β -Arg74, the protein tyrosine phosphatase non receptor type 22 (PTPN22), cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), CD25, and CD40 (40).

TRAb is highly sensitive (97%) and specific (98%) for the diagnosis of GD. Its presence also predicts extra-thyroid

complications of GD and neonatal thyrotoxicosis in the offspring of females planning for pregnancy (38).

Antibodies to thyroglobulin, thyroid peroxidase, sodium-iodide symporter are also present in GD but are not diagnostic.

Sub-acute thyroiditis

Sub-acute thyroiditis is an inflammatory disease of the thyroid, thought to occur following a viral infection. This is also called de Quervain thyroiditis and subacute granulomatous thyroiditis. It is commoner among young and middle aged females (41).

3.3. Clinical features of thyrotoxicosis

Clinical presentation of thyrotoxicosis depends on the severity, underlying cause and age of onset.

Among elderly, presentation can be atypical, in whom apathy or depression could be the only symptom (42).

3.3.1. Common clinical presentations of thyrotoxicosis

Important effects of excess TH occur within the cardiovascular, neuromuscular and ocular systems (Table 3.3).

Table 3.3. Common clinical presentations of thyrotoxicosis

Cardiovascular manifestations	Neuromuscular manifestations	Ocular manifestations	Others
Sinus tachycardia Systolic hypertension Atrial flutter Atrial fibrillation	Hyperactivity and hyper-reflexia Anxiety Tremors Fatigue Proximal muscle weakness Disturbed sleep	Lid lag and lid retraction Proptosis* Eye lid swelling* Conjunctival injection and chemosis* Ophthalmoplegia*	Weight loss despite increased appetite Warm and moist skin Menstrual disturbances Tachypnoea

* These clinical manifestations are characteristic of Graves orbitopathy (GO).

3.3.2. Clinical features indicating the aetiology

Clinical features suggesting a specific aetiology should be identified (Table 3.4).

Table 3.4. Characteristic clinical features favouring an aetiology in patients with thyrotoxicosis

Aetiology	Characteristic clinical features
Graves disease	Usually young female Diffuse goitre with bruit Graves orbitopathy Pretibial myxoedema Thyroid acropachy
Toxic multinodular goitre	Usually older female Long standing nodular goitre
Toxic adenoma	Nodular goitre / solitary nodule
Subacute thyroiditis	Following a viral illness / upper respiratory infection Anterior neck pain: may radiate to throat, ears, jaw and upper chest Systemic manifestations: fever, malaise, fatigue, myalgia and anorexia Tender diffuse goitre (37)

3.4. Evaluation of thyrotoxicosis

3.4.1. Screening for thyrotoxicosis

Box 3.1 lists patient categories that should be screened for thyrotoxicosis.

3.4.2. Diagnosis of thyrotoxicosis

Serum TSH alone is adequate for screening as it has a high sensitivity for the diagnosis of thyrotoxicosis. A normal TSH rules out thyrotoxicosis.

Serum FT4 level along with serum TSH can be used in initial evaluation, particularly when having to do a second test is inconvenient for the patient.

Serum TT3 should be done if FT4 is normal and TSH is suppressed, to rule out T3 toxicosis. TT3 assay is more

reliable and less variable than FT3 (37). When TT3 is not available, FT3 can be used.

Box 3.1. Indications for screening for thyrotoxicosis

- Patient with clinical features of thyrotoxicosis (see table 3.3)
- Patients with suspected secondary osteoporosis, atrial fibrillation or other tachyarrhythmias
- Patients with thyroid eye signs or features of GO

Figure 3.1. Interpretation of thyroid function test in patients with suspected thyrotoxicosis

Note: Acute non-thyroid illnesses can cause a low normal TSH with low normal FT4. TFT should be repeated in few weeks after resolution of the illness.

FT4: free thyroxine, T3: triiodothyronine (free or total)

3.4.3. Supportive tests for evaluation of thyrotoxicosis

All patients with thyrotoxicosis (overt or subclinical) should be evaluated for aetiology and complications.

Table 3.5. Supportive investigations for evaluation of thyrotoxicosis

Investigation	Indication	Relevance	Action
Full blood count	For all	Neutropaenia may occur with thyrotoxicosis Neutrophil leucocytosis is seen in subacute thyroiditis	If neutrophil count is $< 1000 / \text{mm}^3$, do not start ATDs
Liver enzymes and bilirubin	For all	Thyrotoxicosis may cause cholestasis and transaminitis	If liver enzymes are greater than 5 times the ULN, do not start ATDs
12 lead ECG with rhythm strip	For elderly or if clinically indicated	Tachyarrhythmia Atrial fibrillation	<ul style="list-style-type: none"> Heart rate control with BBs Standard management of AF If ECG is normal, but has embolic events, suggest long term ECG monitoring in liaison with cardiology / cardiac electrophysiology
2D echocardiogram	Clinically suspected HF	<ul style="list-style-type: none"> To detect thyrotoxic cardiomyopathy Establish baseline cardiac function and rule out other causes for HF 	Correction of thyrotoxicosis and symptomatic management of HF in liaison with cardiology
DXA scan	For adults > 65 years / with other risk factors for osteoporosis	Thyrotoxicosis is a cause for low BMD	<ul style="list-style-type: none"> Treatment of thyrotoxicosis Optimize calcium and vitamin D intake Consider anti-resorptives *

AF: Atrial fibrillation, ATD: Anti thyroid drugs, BBs: beta blockers, BMD: Bone mineral density, DXA: dual-energy X-ray absorptiometry, ECG: electrocardiogram, HF: heart failure, ULN: upper limit of normal

*according to osteoporosis guidelines

Suggested pathway for evaluation of thyrotoxicosis is summarized in figure 3.2.

3.5. Management of thyrotoxicosis

Treatment of thyrotoxicosis is aimed at:

1. Symptom relief
2. Specific treatment
3. Treatment of complications

3.5.1. Symptom relief

Symptoms of thyrotoxicosis are treated with beta blockers (BB), irrespective of the aetiology, aiming to maintain

heart rate less than 90 beats per minute. When BBs are contraindicated, non-dihydropyridine calcium channel blockers (CCB) can be used (Table 3.6). Once FT4 is normalized, BBs / CCBs can be discontinued.

3.5.2. Specific treatment

Anti-thyroid drugs (ATD), radioactive iodine therapy (RAI) or thyroidectomy are options for treatment of hyperthyroidism. Table 3.7 summarizes a comparison of these modalities.

Figure 3.2. Evaluation for aetiology in a patient with thyrotoxicosis

¹ Presence of thyroid eye signs in a patient with thyrotoxicosis and diffuse goitre on examination confirms the diagnosis of Graves disease and ultrasound is not essential in such patients

All clinically nodular goitres should be evaluated with an ultrasound to determine the risk of malignancy.

² TT3:TT4 ratio > 20 ng/mcg or FT3:FT4 ratio > 30 pg/ng suggests GD (43). FT3:FT4 ratio > 30 pg/ng is 87.0% sensitive and 62.5% specific to differentiate GD from thyroiditis (44).

GD: Graves disease, MNG: multinodular goitre, TA: Toxic adenoma, TRAb: TSH receptor antibodies, US: ultrasound

Table 3.6. Beta blockers and calcium channel blockers for treatment of symptomatic thyrotoxicosis

Agent	Dose	Frequency	Remarks
Propranolol	10-40 mg	2 – 3 times a day	Non-selective β antagonist
Atenolol	25-100 mg	1 – 2 times a day	Relatively β -1 selective antagonist Avoid in pregnancy
Metoprolol	25 – 50 mg	2 – 3 time a day	Relatively β -1 selective antagonist Extended release preparations can be given 1 – 2 times a day
Verapamil	80 – 160 mg	3-4 times a day	Maximum dose 480 mg per day
Diltiazem	30 – 120 mg	3-4 times a day	Maximum dose 480 mg per day

Adapted from American Thyroid Association guidelines for the management of thyrotoxicosis 2016 (37).

Table 3.7. Specific treatment options available for management of hyperthyroidism

	Anti-thyroid drugs	Radio-active iodine	Thyroidectomy
Advantages	Rapid control within weeks to months	Definitive cure of thyrotoxicosis in most with minimum adverse effects	Definitive cure of thyrotoxicosis with immediate disease control
Disadvantages	<ul style="list-style-type: none"> • Risk of recurrence / need for lifelong therapy with toxic nodules • Drug side effects 	<ul style="list-style-type: none"> • Need for lifelong LT4 • Risks of radiation (should avoid pregnancy for 6-12 months. Men should avoid fathering for 3-4 months) • Several months to establish control • May worsen GO 	<ul style="list-style-type: none"> • Surgical complications • Risk of recurrent laryngeal nerve palsy • Risk of hypoparathyroidism • Needs lifelong LT4
Compelling indications	<ul style="list-style-type: none"> • Need for rapid control • Pregnant • Unfit for surgery • Institutionalized / unable to follow post RAI precautions • Limited life expectancy • Moderate to severe GO • Mild disease, small goitre, negative or low TRAb titre 	<ul style="list-style-type: none"> • Unfit for surgery • ATD intolerance / contra-indicated / failure • Periodic paralysis • Heart failure • Pulmonary hypertension • GD with low chance of remission 	<ul style="list-style-type: none"> • Planning pregnancy within 6 – 12 months • Moderate to severe active GO • Suspicion of cancer* • Large goitre > 80 g • Compression symptoms • Hyperparathyroidism needing surgery • Retrosternal goitre
Contra-indications	<ul style="list-style-type: none"> • Major adverse events with ATDs in the past 	<ul style="list-style-type: none"> • Pregnancy / planning for pregnancy within 6 months • Lactation • Inability to comply with safety precautions • Suspected thyroid cancer • Moderate to severe active GO • Retrosternal goitre 	<ul style="list-style-type: none"> • Unfit for surgery • Pregnancy – relative contraindication. Can do in 2nd trimester, still increased risk of preterm delivery, recurrent laryngeal nerve palsy and hypoparathyroidism • Lack of access to high volume surgeon

*Nodule > 4cm, nodule with relatively low uptake, cytology suspicious or indeterminate

ATD: anti-thyroid drugs, GD: Graves disease, GO: Graves orbitopathy, RAI: radio-active iodine, TRAb: TSH receptor antibodies

Anti-thyroid drugs – Thionamides

ATDs are the preferred first line agent for hyperthyroidism of any aetiology. A guide for starting dose is given in table 3.8.

Adverse effects of thionamides

Most adverse effects of thionamides occur within 3-12 weeks of treatment initiation. Table 3.9 summarizes their characteristics and management.

Table 3.8. Starting dose of carbimazole

Free T4 level	Carbimazole (mg/day)*
1 – 1.5 × ULN	10 – 15
1.5 – 2 × ULN	15 – 30
2 – 3 × ULN	45 – 60

ULN: Upper limit of normal

* When higher doses are required, administration in divided doses may help faster normalization of FT4.

Table 3.9. Adverse effects of thionamide anti-thyroid drugs

Adverse effect	Description	Action
Skin rash (3-6%)	Maculo-papular. Pruritic in some	<ul style="list-style-type: none"> Minor reaction – continue ATD, brief course of antihistamine Major reactions – stop ATD, offer alternative treatment
Agranulocytosis (0.11 – 0.27%)	Absolute neutrophil count < 500 / mm ³ Dose dependent and reversible	<ul style="list-style-type: none"> Stop ATD Screen for and treat sepsis with broad spectrum antibiotics Consider G-CSF and glucocorticoids Avoid thionamides for life (45). Offer alternative treatment* Neutrophil 1000 – 1500 / mm³: may continue ATD with close monitoring of neutrophil counts
Hepatotoxicity (0.1 – 4.0%)	Dose dependent. Carbimazole / methimazole causes cholestasis. PTU causes hepatitis.	<ul style="list-style-type: none"> If liver enzymes are > 3 times the ULN or show a progressive rising trend, temporarily discontinue ATD and monitor LFT at least once a week. Treat thyrotoxicosis with non-thionamide ATD or other definitive treatment strategy. When liver enzymes return to normal, alternative thionamide ATD can be considered, unless the liver injury was severe.
Teratogenicity	3-4% with carbimazole (more severe: tracheo-oesophageal fistula, choanal atresia, aplasia cutis) & 2-3% with PTU (milder: pre-auricular sinus, renal tract anomalies)	<ul style="list-style-type: none"> Use PTU up to 16 weeks. Switch back to carbimazole thereafter (to avoid PTU associated liver injury)

ATD: anti-thyroid drugs, G-CSF: granulocyte colony stimulating factor, PTU: propylthiouracil, RAI: radio-active iodine, ULN: upper limit of normal, LFT: liver function test

*alternative treatment: non-thionamide ATDs / RAI / surgery

All patients commenced on ATD should have baseline full blood count, liver enzymes and bilirubin levels measured.

Routine monitoring of these investigations are not beneficial since side effects are abrupt in onset, almost always symptomatic and affect only a minority of patients.

Patients should be provided written advice to stop ATD and report urgently if any of the following develops while on ATDs:

- Sore throat, fever, other symptoms of an infection
- Jaundice, pale stools, pruritus, abdominal pain, vomiting, anorexia
- Skin rash

Non-thionamide ATDs

Non-thionamide ATDs can be used in following situations:

1. Maximum tolerated thionamide dose fails to achieve euthyroidism
2. Thionamides are contraindicated due to severe adverse effects

3. Need for rapid reversal of thyrotoxicosis – thyrotoxic storm, pre-operative setting

In these circumstances, patients should be referred to a specialist to consider non-thionamide therapies.

Radioactive iodine therapy (RAI)

RAI offers a non-invasive definitive therapy by ablating the hyperfunctioning thyroid tissue.

It is administered as a single oral capsule containing radioactive iodine-131 isotope which concentrates in the hyperfunctioning thyroid gland.

If the gland is diffusely hyperfunctioning (as in GD), the entire gland will take up iodine. In toxic MNG, often the rest of the gland is hypo-functioning and therefore, most of the dose will accumulate in the hyper-functioning nodule and rest of the gland will be relatively preserved.

Patient preparation for RAI is shown in box 3.2. Expected outcomes are summarized in table 3.10. Follow up plan is outlined in box 3.3.

Box 3.2. Patient preparation for RAI (46),(37),(47)

- ☐ Informed written consent. Emphasize the need to
 - ✓ avoid pregnancy for 6-12 months / fathering for 3-4 months.
 - ✓ stop lactation for 6-12 weeks before RAI and not to recommence until next pregnancy (55)
 - ✓ avoid close contact with children and pregnant mothers for several days after therapy (specific recommendation should be according to radio-oncology protocols)
 - ✓ some may need long term thyroxine
- ☐ Exclude pregnancy - Negative pregnancy test within 72 hours before receiving RAI irrespective of contraceptive use (55).
- ☐ Minimize risk of thyrotoxic crisis after RAI
 - ✓ Try to achieve euthyroidism
 - ✓ Give BBs irrespective of thyroid status, unless contraindicated (46).
 - ✓ ATDs can be used to reduce the risk, but will also reduce the efficacy of RAI (56).
- ☐ Discontinue thionamide ATDs
 - ✓ This is to allow iodine trapping in thyroid follicular cells
 - ✓ Stop carbimazole 5-7 days and propylthiouracil 2-3 days prior to RAI
 - ✓ Those can be resumed 3-7 days after RAI, especially in patients who are at risk of worsening thyrotoxicosis (46).
 - ✓ Lithium carbonate can be continued during RAI as it may improve the outcome by prolonging the iodine trapping within thyroid tissue.
- ☐ Optimize other medical co-morbidities

Table 3.10. Outcomes of radioiodine therapy according to the aetiology of thyrotoxicosis
(48)(49)(50)(51)(37)(52)(45)

Aetiology	Resolution of thyrotoxicosis	Development of hypothyroidism
Graves disease	70 – 90% by 1 year	In 40% by 8 weeks and 80% by 16 weeks
Toxic adenoma	93.7% (overall)	In 28% by 5 years
Toxic multinodular goitre	81.1% (overall)	In 4% by 5 years

Box 3.3. Follow up investigations after RAI for hyperthyroidism

1	Repeat TFTs 1-2 months after RAI and 4-6 weekly thereafter until stabilized
2	Once hypothyroidism develops, thyroxine replacement therapy should be commenced.
3	If thyrotoxicosis persists beyond 6 months, a repeat dose of RAI should be considered.

Adverse effects of RAI

- Thyroiditis (often mild and transient)
- Worsening of GO
- Sialadenitis, mucositis, dry eyes / excessive tearing, dry mouth, altered taste sensation

Some studies have raised concerns about an association between solid organ malignancy related mortality and RAI, but, this remain inconclusive due to methodological limitations (53)(54). Therefore, no recommendations are made for routine screening for cancer among RAI

recipients, beyond the recommendations for general population.

Thyroidectomy

Thyroidectomy helps to rapidly achieve cure of hyperthyroidism.

Potential complications of thyroidectomy are listed in box 3.4

Patients with hyperthyroidism undergoing thyroidectomy should be optimized as described in table 3.12.

Box 3.4. Complications of thyroidectomy*

1	Permanent hypothyroidism requiring lifelong thyroxine replacement in all
2	Damage to recurrent laryngeal nerve causing hoarseness of voice (less than 5.8%)(55)(56)
3	Damage to parathyroid gland causing hypoparathyroidism, often transient but rarely permanent (1.9%)(57)
4	Complications related to surgery (haematoma, permanent scar) and general anaesthesia

*In high volume centres, surgical complications are rare. However, these considerations should be discussed with the patient before surgery. Following thyroidectomy, replacement doses of levothyroxine can be commenced from first post-operative day. Consider delaying levothyroxine if pre-operative control of thyrotoxicosis was poor.

Table 3.12. Preparation for thyroidectomy

1	Written informed consent	• Discuss potential complications (box 3.4) including need for lifelong thyroxine after surgery
2	Achieve euthyroid/ near-euthyroid state	• To minimize the incidence and severity of peri-operative thyrotoxic crisis • ATDs can be discontinued after the morning doses on the day of surgery
3	Check and correct calcium and vitamin D level	• To minimize risk and severity of post-operative hypocalcaemia and hungry bone syndrome
4	Pre-operative Lugol's iodine	• Helps to control hyperthyroidism as well as reduce vascularity of the thyroid gland
5	Seek specialist opinion when patients undergo surgery before achieving good biochemical control of thyrotoxicosis

Figure 3.3. Choice of treatment in patients with hyperthyroidism
ATD: anti-thyroid drugs, GO: Graves orbitopathy, TRAb: TSH receptor antibodies

3.6. Graves orbitopathy

3.6.1. Epidemiology

The incidence of Graves orbitopathy (GO) is 42.2 per million per year (20.1% of the incidence of GD)(58). The incidence of moderate to severe and very severe GO is 16.1 per million per year in the general population, with a female: male ratio of 5:1 and peak incidence between 40 and 60 years (59)(60).

3.6.2. Pathophysiology

TRAbs (from plasma cells) and cytokines (from T cells) activate retro-ocular fibroblasts and adipocyte which bear TSH receptors (61).

Fibroblasts secrete glycosaminoglycans (GAG) such as hyaluronic acid (62)(63). Hydrophilic GAGs cause fluid accumulation, muscle swelling, increased pressure within the orbit and impaired venous drainage. These changes, together with retro-ocular adipogenesis, displace the eyeball forward and cause extra-ocular muscle dysfunction.

3.6.3. Evaluation of GO

Selecting the most appropriate treatment for individual patients depends on the activity and severity of the eye changes.

Assessment of disease activity

Disease activity can be assessed using Clinical Activity Score (CAS) (box 3.5). A CAS $\geq 3/7$ is indicative of active GO (64).

Assessment of disease severity

Disease severity can be measured according to EUGOGO classification (Table 3.13).

Severity is rated as mild, moderate to severe and sight threatening (or very severe).

Visual acuity, colour vision, corneal and retinal assessment should be performed to recognize sight threatening GO.

Consider orbital imaging (MRI or CT with contrast) when diagnosis is doubted or for surgical planning.

Box 3.5 Clinical Activity Score (CAS) for assessment of disease activity of GO

Spontaneous retrobulbar pain
Pain on attempted upward or downward gaze
Redness of eyelids
Redness of conjunctiva
Swelling of caruncle or plica
Swelling of eyelids
Swelling of conjunctiva (chemosis)
Add 1 mark for each positive feature. Inactive GO = CAS < 3, Active GO = CAS ≥ 3

Assessment of quality of life

Impact of GO on the individual's quality of life (QoL) and psychosocial well-being should be assessed.

The use of GOQoL questionnaire, a disease-specific and validated tool, is recommended in routine clinical practice (65).

Table 3.13. EUGOGO severity classification of GO

Disease severity	Description	Features
Mild GO	GO has only a minor impact on daily life, insufficient to justify immunosuppressive or surgical treatment.	One or more of the following: <ul style="list-style-type: none"> • minor lid retraction (<2 mm) • mild soft-tissue involvement • exophthalmos <3 mm above normal for race and gender • no or intermittent diplopia • corneal exposure responsive to lubricants
Moderate-to-severe GO	Non-sight-threatening GO with eye disease causing sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive).	Two or more of the following: <ul style="list-style-type: none"> • 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 GO (very severe GO)	Likely to lose vision if not treated urgently	Dysthyroid optic neuropathy (DON) and / or corneal breakdown

3.6.4. .Management of GO

General measures in management of GO

Refer for specialized management

Patients with GO should be referred to a specialized centre providing endocrinology and ophthalmology expertise, except for the mildest forms that improve with normalizing thyroid status and local lubricants (65).

Elevation of head-end while sleeping and diuretics can help to relieve periorbital oedema

Table 3.14. General measures in the management of GO

Action	Description	Recommendation
Stop smoking	Smoking increases the severity (66)(67), risk of progression and de novo occurrence of GO after RAI therapy (68) and delays or mitigates the benefits of immunosuppressive treatment for GO (69). Smoking cessation improves outcome of GO (70).	All patients with Graves disease should be advised to stop smoking. Arrange for support if needed.
Restore euthyroid state	Hypo and hyperthyroid states worsen GO. ATD and surgery do not have a significant effect (68). RAI may worsen GO (71) (72)	Offer steroid prophylaxis before RAI for patients at risk for deterioration of GO (table 3.15)
Topical therapy	increased palpebral fissure width, exophthalmos, slow blink rate, lid lag, lagophthalmos and poor Bell's phenomenon predisposes to dry eyes and corneal damage	Topical artificial tears to prevent drying (65)

. RAI therapy can worsen GO. Risk can be reduced by administration of glucocorticoids, starting 1-3 days after RAI (table 3.15). Avoid RAI in patients with active moderate to severe or sight threatening GO.

Specific management

Specific management of GO will depend on the disease activity and the severity as described in figure 3.4.

In addition to supportive measures, specific treatment options for GO of different severity categories are

summarized in table 3.17. Seek specialist advice before administration of immunosuppressive therapies.

Table 3.15. Steroid prophylaxis with RAI treatment in patients with GO

Risk category	Description	Glucocorticoid use
Very low	No GO Inactive GO, euthyroid and non-smoking	Not necessary
Low	Active mild GO. No risk factors for deterioration	Oral prednisolone 0.2 mg/kg body weight per day for 6 weeks and tail off over 1-2 months (73)
High	Active mild GO, with risk factors for deterioration	Oral prednisone 0.3-0.5 mg /kg body weight/daily for 1 month and tail off over 2 -3 months

Risk factors for GO deterioration are smoking and high TRAb titres.

Consider risks of glucocorticoids including deterioration of diabetes control, risk of infections, osteoporosis and psychiatric illnesses patients with active moderate to severe GO or sight threatening GO.

Figure 3.4. Treatment options in Graves Orbitopathy (adapted from European Thyroid Association / European Group on Graves Orbitopathy guidelines, 2016). IV GC: intravenous glucocorticoids

Table 3.16. Specific management of GO according to severity and activity

Severity	Treatment	Remarks
Mild GO	<ul style="list-style-type: none"> Sodium selenite 100 µg twice a day for 6 months Consider immunosuppressive therapy for active disease and orbital surgery for inactive disease 	Selenium improves eye manifestations, QoL and prevents GO progression to severe stages (74).
Active moderate to severe GO	<ul style="list-style-type: none"> IV methyl prednisolone (MP) 0.5 g weekly for 6 weeks and 0.25 g weekly for 6 weeks (4.5g in total) (75)(76)(77). Consider 2nd line options for partial / no response and for recurrences (table 3.17). 	<ul style="list-style-type: none"> Cumulative dose of IV MPs should not exceed 8.0 g Avoid IV MP in patients with recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity or psychiatric disorders Control diabetes and hypertension before IV MP
Sight threatening GO	<ul style="list-style-type: none"> IV MP 0.5 - 1 g for 3 consecutive days or on alternate days during the 1st week. Can be repeated after a week (78)(79). Surgical orbital decompression within 2 weeks if response is poor. 	Treat as an emergency to prevent blindness
Inactive moderate to severe GO	<ul style="list-style-type: none"> Elective rehabilitative surgery after 6 months of disease inactivity, when visual functions and / or QoL is affected 	Refer to a centre with expertise for orbital surgery

Table 3.17. Second line treatment of moderate-severe and active GO

Second line therapy	Remarks
IV GCs	If the patient tolerates and cumulative dose of MP does not exceed 8g.
Mycophenolate	250 mg oral twice a day for 6 months (80).
Mofetil	
Orbital radiotherapy	As effective as oral GCs, potentiates the effect of oral GCs and improves diplopia and eye muscle motility (81)(82).
Cyclosporine	5 – 7.5 mg/kg for up to one year (83).
Rituximab	Can be used as a second line treatment(84), especially in patients with a relatively short disease duration(85).
	1000 mg IV two doses two weeks apart.
Tocilizumab	IV tocilizumab 8 mg/kg 4 weekly for 16 weeks
Teprotumumab	Human monoclonal antibody inhibitor of the insulin-like growth factor-1 (IGF-1) receptor This is the first therapy to be reported to reduce proptosis in GO (86). Administered every three weeks as an IV infusion (10 mg/kg initial dose, then 20 mg/kg)

GC: Glucocorticoids, MP: methyl prednisolone

3.6.5. Treatment of other extra-thyroid manifestations of GD

Therapy with topical steroids applied under an occlusive plastic dressing for 3-10 weeks has been helpful for pretibial myxoedema. In severe cases, pulse glucocorticoid therapy may be tried. No therapy has been proven to be effective for thyroid acropachy.

3.7. Evaluation and management of subacute thyroiditis

3.7.1. Natural course of the disease

Thyrotoxic features are seen in about 50% (transient and resolves in about 2-8 weeks)

This will be followed by a hypothyroid phase lasting for about 2-8 weeks. Minority will develop permanent hypothyroidism (87)(88).

3.7.2. Evaluation of sub-acute thyroiditis

Useful investigations and expected results are summarized in table 3.18.

In some patients with predominant thyrotoxic features differentiation from Graves disease would be difficult.

Following would guide the differentiation in clinical practice (Table 3.19).

Table 3.18. Summary of evaluation of sub-acute thyroiditis

Test	Result
TFT	Initially elevated FT4 and FT3 with low TSH Later TFT may show overt or subclinical hypothyroidism followed by normalization
Inflammatory markers	Elevated ESR, CRP. Neutrophil leucocytosis
Thyroxine binding globulin	Elevated
Anti-thyroid antibodies	Negative in many
Ultrasound thyroid	Mildly enlarged gland with hypoechogenicity and normal flow in colour Doppler (62)
Radio-iodine or technetium uptake scan	Reduced uptake (62)(87)

Table 3.19. Features differentiating subacute thyroiditis from Graves disease

	Sub-acute thyroiditis	Graves disease
Thyroid hormones	Markedly elevated free T4 compared to free T3 (FT3/FT4 < 30 pg/ng)	Greater rise of free T3 (FT3/FT4 > 30 pg/ng)
Laboratory parameters	Elevated ESR, CRP, White cell count and mild anaemia	Not usually seen
TRAb	Negative	Positive
Colour Doppler	Reduced blood flow	Increased blood flow
Radio-iodine or technetium uptake	Reduced	Increased

3.7.3. Management of sub-acute thyroiditis

Table 3.20. Summary of the management of sub-acute thyroiditis

Monitor disease progression	Monitor thyroid functions to detect disease evolution over time	
Treat features of local / systemic inflammation	Minimal symptoms	May be managed conservatively
	Mild neck pain and mild systemic symptoms	High dose NSAIDs (e.g. Ibuprofen 1200- 3200mg/day in divided doses)
	severe symptoms or poor response to NSAIDs within 2-3 days	Oral steroid therapy <ul style="list-style-type: none"> • Prednisolone 40mg/ day and tapered slowly within 2-8 weeks or • Prednisolone 15mg/day to taper within 6 weeks and increase only if inadequately responding (89).
Treat thyroid dysfunction	Symptoms of hyperthyroidism	<ul style="list-style-type: none"> • Non-selective BBs / CCBs • No place for ATDs or RAI
	During hypothyroid phase	Treat with LT4

Key recommendations – Thyrotoxicosis and Graves orbitopathy

Diagnosis

Perform TSH in patients with clinical features of thyrotoxicosis, premature unexplained osteoporosis, tachyarrhythmias or suspected Graves orbitopathy. If suppressed, perform free T4 and where necessary total T3 / free T3 (figure 3.1). All patients with thyrotoxicosis should have full blood count, liver enzymes and bilirubin levels tested. Consider ECG, 2D echo and DXA scan where appropriate (table 3.5). Assess clinically and consider ultrasound scan of thyroid, TSH receptor antibodies and thyroid uptake scan to establish the aetiology (figure 3.2).

Treatment of thyrotoxicosis

Treat symptoms of thyrotoxicosis with beta blockers or calcium channel blockers (table 3.6).

Use anti-thyroid drugs for control of hyperthyroidism. Consider definitive therapy with radioiodine or thyroidectomy early where appropriate (table 3.7 and figure 3.3).

Determine starting dose of ATDs according to the FT4 level at presentation (table 3.8).

Advise patients (preferably in writing) regarding neutropaenia, hepatotoxicity and skin rash (table 3.9).

De Quervain thyroiditis – Offer symptomatic therapy for thyrotoxicosis and NSAIDs or short course of glucocorticoids for neck pain and / or systemic inflammatory symptoms. Periodically monitor TFT to recognize progression to hypothyroidism.

Follow up – thyrotoxicosis

Monitor response to ATDs by clinical assessment and FT4 levels.

Management of Graves orbitopathy

Assess activity, severity, vision (acuity, colour vision) and quality of life (section 3.6.3)

Consider ultrasound neck, TRAb and MRI orbits for diagnosis and planning treatment

Active GO should be treated with systemic glucocorticoids. Consider second line therapies for more severe disease or if response is poor (section 3.6.4).

Refer to specialist

In patients with thyrotoxicosis, refer to a specialist if

- Diagnosis / aetiology of thyrotoxicosis is uncertain
- Control is inadequate with ATDs
- Intolerant of ATDs
- Planning for RAI or thyroidectomy

In patients with Graves orbitopathy,

- All patients except the mildest cases should be referred for specialized care
- Refer to ophthalmologist for visual assessment and / or surgery (urgent decompression for sight threatening GO or elective rehabilitative surgery)

4.0 THYROID DYSFUNCTION AND PREGNANCY

4.1 Introduction

Increased demand for TH during the pregnancy is met by the compensatory mechanisms of HPT axis in the presence of adequate thyroid reserve (90)(91). Important

physiological alterations of the thyroid gland and its functions are illustrated in the figure 4.1.

4.2. Interpretation of TFT during pregnancy

Changes in TFTs during normal pregnancy are summarized in table 4.1

Figure 4.1. Pregnancy associated alterations in thyroid physiology

TBG: thyroid binding globulin, TH: thyroid hormone

4.3. Hypothyroidism in pregnancy

Impaired or inadequate adaption to the increased physiological demand due to pathological conditions

causes hypothyroidism leading to adverse maternal and foetal consequences

Table 4.1. Alteration of TFT due to physiological changes in pregnancy (90)(91)(92)(93)(94)

Physiological alteration	Interpretation
Increased serum hCG levels in the 1st trimester (peak in the 10th week of pregnancy)	<ul style="list-style-type: none"> hCG stimulates TSHR due to structural homology with TSH molecule Elevated TH levels and suppressed TSH levels during 1st trimester
Elevation of TBG and reduction of serum albumin levels	<ul style="list-style-type: none"> Elevated TT4 and TT3 TT4 is 1.5 times higher than non-pregnant reference range FT4 assay is highly variable and should use population specific reference range if available
Lowered reference range of the TSH levels due to multiple factors <ul style="list-style-type: none"> Ethnicity Genetics Geography TPO antibody status Iodine status TSH assay use 	Following trimester specific reference ranges are recommended according to available local and regional data <ul style="list-style-type: none"> 1st Trimester : 0.1- 2.5 mIU/L 2nd Trimester: 0.1- 3.0 mIU/L 3rd Trimester: 0.1- 3.0 mIU/L

hCG: human chorionic gonadotrophin

Table 4.2. Adverse foetal and maternal consequences of hypothyroidism in pregnancy

Overt hypothyroidism	Subclinical hypothyroidism and isolated hypothyroxinaemia of pregnancy
<ul style="list-style-type: none"> Foetal <ul style="list-style-type: none"> Miscarriages Premature birth Low birth weight Impaired neurocognitive development Maternal Gestational hypertension (90)(91) 	<ul style="list-style-type: none"> Preterm birth, miscarriages TPO antibody positivity further increases the risk LT4 replacement has not shown any benefit of reducing the risk (92)(95)(96)(97) <p>Pre-eclampsia, placental abruption</p>

4.3.1. Evaluation

Screening

Universal screening cannot be recommended due to unavailability of strong evidence of benefit and dynamicity of TFT throughout the pregnancy. Screening is

recommended in high risk groups [section 2.5, box 2.1](90)(91) .

Diagnosis

Hypothyroidism in pregnancy is considered to be a disease spectrum (Table 4.3).

Table 4.3. Diagnosis of hypothyroidism in pregnancy

Overt hypothyroidism	Elevated TSH* and a decreased FT4
Subclinical hypothyroidism	Elevated TSH* levels with normal FT4
Isolated hypothyroxinaemia	Normal TSH level with low FT4

*Above the upper limit of trimester specific reference range

4.3.2. Management

Overt hypothyroidism

Table 4.4. summarises management of overt hypothyroidism in pregnancy.

Subclinical hypothyroidism

Due to conflicting evidence on benefit, treatment of SH is recommended to be individualized. Algorithm in figure 4.2 gives a guide to treatment (Figure 4.2).

Table 4.4. Management of overt hypothyroidism in pregnancy(90)(98)(99)

Hypothyroidism diagnosed during pregnancy
<ul style="list-style-type: none"> Start LT4 2.33 µg/kg/day
Hypothyroidism diagnosed before pregnancy
<ul style="list-style-type: none"> Patients on full replacement dose require 40-50% dose increment In patients with autoimmune hypothyroidism, 25% increment may be adequate Increase the dose as soon as pregnancy is suspected (1st missed period) Doubling the dose on weekend days is sufficient to achieve a 30% dose increment

Figure 4.2. Treatment algorithm for subclinical hypothyroidism in pregnancy (90)(98)(95)

* If TPO antibody testing is not available consider treatment with LT4 if TSH is between 2.5 - 4 mIU/L and should start treatment if TSH is above 4 mIU/L. ULN PR: upper limit of normal for pregnancy specific reference range

Isolated hypothyroxinaemia

LT4 therapy is not recommended routinely due to unavailability of evidence of benefit(90)(92). Adequacy of iodine intake should be ensured (100).

4.3.3. Follow up and monitoring

Goal of treatment

Maintaining TSH level within lower half of trimester specific reference range or <2.5 mIU/L is recommended (90)

Monitoring

Measure serum TSH approximately every 4 weeks until mid-gestation and at least once near 30 weeks of gestation (90)

4.3.4. Management of hypothyroidism during post-partum period

Consider following factors:

- LT4 requirement decreases to pre-pregnancy level after delivery (101).

- Subclinical hypothyroidism in pregnancy is usually transient (102).
- Some may develop exacerbation of autoimmunity, causing transient thyrotoxicosis due to post-partum thyroiditis (103)(104).
- Positive TPO antibodies predict risk of persistent hypothyroidism (105).

Table 4.5 describes a guide in managing patients with hypothyroidism during post-partum period.

TFTs should be rechecked at around six weeks postpartum and treatment adjusted accordingly.

Table 4.5. Management of hypothyroidism during post-partum period

Overt hypothyroidism	
Diagnosed before pregnancy	Return to pre-pregnancy dose provided the patient was euthyroid with that dose
Diagnosed during pregnancy	Two thirds of the dose in third trimester
Subclinical hypothyroidism	
Higher TSH, positive TPO Ab	Continue at half of the third trimester dose (101)(106)
Lower TSH, negative TPO Ab, low LT4 dose requirement during pregnancy ($\leq 25 \mu\text{g/day}$)	Stop treatment, follow up with TFT

4.4. Hypothyroidism and thyroid-autoimmunity in fertility management

Table 4.6. Hypothyroidism and thyroid autoimmunity in fertility management

Thyroid disorder	Fertility issue	Impact	Intervention
Overt hypothyroidism	Subfertility	Impairs fertility (90)	Treatment with LT4 to achieve euthyroidism
	Undergoing ART	Impairs ART success	Treatment with LT4 to achieve euthyroidism
Subclinical hypothyroidism	Subfertility	No clear evidence on effect and benefit of treatment	Consider low dose LT4 since TH rise may be inadequate in pregnancy (90)
	Undergoing ART	Treatment may be beneficial when TSH > 4 mIU/L	Consider low dose LT4 therapy
Thyroid autoimmunity (positive thyroid antibodies) with euthyroidism	Subfertility	There is no clear evidence on association between fertility and thyroid autoimmunity or benefit of treatment (107)(108)	No recommendations on treatment
	Undergoing ART	Most of the high quality studies do not show benefit of treating these patients.	Treatment not recommended

ART: Assisted reproductive technology

During ovarian hyperstimulation for ART there would be alteration in TFT due to several reasons including increased thyroid binding globulins and increased hCG. Therefore, it is recommended to perform thyroid function tests either before or 1-2 weeks after ovarian hyperstimulation.

4.5. Hyperthyroidism in pregnancy

4.5.1. Causes of hyperthyroidism in pregnancy

Gestational thyrotoxicosis and GD are the two most common aetiologies. A guide for clinical differentiation and management are summarized in table 4.7.

Table 4.7. Comparison of gestational thyrotoxicosis and Graves disease

	Gestational thyrotoxicosis	Graves disease (GD)
Clinical presentation	<ul style="list-style-type: none"> Occurs in 1-3% of pregnancies typically in the first half of gestation Associated with hyperemesis gravidarum, hydatidiform mole, multiple gestation, choriocarcinoma Less severe than GD 	<ul style="list-style-type: none"> May present with a diffuse goitre and / or eye signs
	<ul style="list-style-type: none"> Tachycardia, heat intolerance and excessive sweating; could mimic the non-specific symptoms of pregnancy itself Loss of weight despite intact appetite, anxiety, and tremors may be seen in both the conditions. 	
Investigations	Serum TSH suppressed ($<0.1\text{mU/L}$) or undetectable ($<0.01\text{mU/L}$) and a FT4 & / or FT3 (or TT4 & / or TT3) exceeds the pregnancy specific normal range	
	Serum T4 disproportionately elevated than T3	<ul style="list-style-type: none"> Serum T3 disproportionately elevated than T4 TRAb positive
Management	<ul style="list-style-type: none"> Hydration Antiemetics for vomiting BBs such as metoprolol, propranolol (10-40 mg/ 6-8 hourly) usually for 2-6 weeks ATDs not recommended 	<ul style="list-style-type: none"> Refer section 4.5.2.
Prognosis	Serum FT4 normalizes by 14-18th week of gestation	Improves in latter part of gestation due to a reduction of TRAb levels and rarely, due to the change in activity of TRAb from stimulatory to inhibitory.

ATD: anti-thyroid drugs, BB: beta blockers, TRAb: TSH receptor antibodies

4.5.2. Management of Graves disease in pregnancy

Pregnancy planning

Poor disease control increases the risk of miscarriages, pregnancy induced hypertension, intrauterine growth restriction, preterm labour and maternal congestive cardiac failure.

Practice contraception until stably euthyroid (biochemically euthyroid at least twice, 1 month apart) (37).

Preconception adjustment of treatment

These considerations are summarized in table 4.8

Table 4.8. Pre-conception treatment adjustment

Scenario	Option(s)
Treated with ATD for 12-18 months, euthyroid with small ATD dose (carbimazole 5-10 mg/day), TRAb negative	Stop ATD, monitor TFT 1-2 weekly in first trimester and 2-4 weekly thereafter (90).
On high doses of ATD	Consider RAI / surgery (discuss the need to delay pregnancy) Continue ATD: switch from carbimazole to propylthiouracil Young women, regular cycles: switch when planning for conception Older women / irregular cycles : switch when pregnancy is diagnosed

Treatment during pregnancy

Treatment goals

- TSH: pregnancy specific reference range
- FT4: at or just above trimester specific reference range
- TT4: 1.5 times above the reference range for non-pregnant females

Adjusting therapy

PTU is associated with maternal hepatitis / fulminant liver necrosis / liver failure. Therefore switch back to carbimazole after 16 weeks, after which risk of teratogenicity is minimal (109).

Adverse effects

Teratogenicity (see section 3.5.2, table 3.9)

BB beyond 6 weeks of gestation may increase the risk of foetal growth restriction (110)

Other treatment options

RAI is absolutely contraindicated in pregnant women due to the possible risk of miscarriages, foetal thyroid ablation and birth defects.

Thyroidectomy may be considered in patients who develop allergy or agranulocytosis with antithyroid agents and preferably done during the second trimester

Foetal monitoring

All foetuses of women with GD should be monitored for signs of thyrotoxicosis with foetal heart rate and growth rate (111).

TRAb is a useful predictive marker of foetal hyperthyroidism.

Women with GD and high TRAb levels, even if euthyroid, warrant monitoring for foetal and neonatal hyperthyroidism.

4.6. Thyrotoxicosis during post-partum period

4.6.1. Post-partum thyroiditis

Commonly seen within a year from delivery and the prevalence is around 5% (1.1 – 16.7%) (112).

It is characterized by the occurrence of either transient thyrotoxicosis, transient hypothyroidism, or transient thyrotoxicosis followed by transient hypothyroidism and return to euthyroidism (Figure 4.3) (113). Latter is the classic form.

Pathophysiology

It is an autoimmune disorder associated with TPO antibodies, thyroglobulin antibodies, lymphocyte dysregulation, complement activation, excess natural killer cell activity, high IgG1 and HLA DR3,4,5 (90).

The presence of other autoimmune disorders and previous history of postpartum thyroiditis also increase the risk (114)(115).

Symptoms

In thyrotoxic phase palpitations, fatigue, heat intolerance, and irritability/nervousness are common symptoms.

Hypothyroid patient would complain of impaired concentration, carelessness, dry skin, poor memory, and decreased energy.

However both toxic and hypothyroid phases may be asymptomatic or present with subtle nonspecific symptoms.

The following features could help in differentiating postpartum thyroiditis from GD (113).

Figure 4.3. Clinical presentations of post-partum thyroiditis

Table 4.9. Differentiation of post-partum thyroiditis and GD

Feature	Graves disease	Post-partum thyroiditis
Timing	Majority occurs after 3 months from delivery	Majority occurs within 3 months postpartum
Prevalence	0.2%	4.1%
Unique clinical features	Goitre with a bruit, ophthalmopathy	-
TRAb	Positive	Negative
T3:T4	High	Low
Thyroid uptake scan*	Increased uptake	Decreased uptake

*Thyroid uptake scan should not be performed in lactating mothers. TRAb: TSH receptor antibodies

Management

Management of post-partum thyroiditis is described in the algorithm in figure 4.4.

Figure 4.4. Management of different phases of post-partum thyroiditis

*A decision to tail off levothyroxine may be considered if not planning to conceive by 1 year postpartum.

Key recommendations

Hypothyroidism in pregnancy

Screen for hypothyroidism for routine indications as in non-pregnant populations (section 2.5, box 2.1). Use pregnancy specific reference ranges for diagnosis and monitoring (table 4.1).

Treat overt hypothyroidism with LT4. Starting dose in pregnancy is 2.33 µg/kg/day. For patients stably on levothyroxine prior to conception, increase the pre-pregnancy dose by 30%.

Treatment of subclinical hypothyroidism should be decided considering TPO antibody status and TSH level (figure 4.2).

Monitor TFT monthly till 20 weeks and at least once around 30 weeks. Aim to maintain TSH in trimester specific normal range.

Reduce dose of levothyroxine to pre-pregnant stable dose or two-thirds of last trimester dose (if stabilized during pregnancy) following birth of the child in a female with overt hypothyroidism. Lower doses or withdrawal can be considered in subclinical hypothyroidism (table 4.5). Reassess thyroid functions at six weeks post-partum.

Hypothyroidism, thyroid autoimmunity and fertility

Treatment of overt and subclinical hypothyroidism to achieve euthyroidism is recommended in females with subfertility

There is no recommendation to treat euthyroid females with thyroid autoimmunity and subfertility

Thyrotoxicosis in pregnancy

Graves disease may first manifest during pregnancy. Gestational thyrotoxicosis (table 4.7) and post-partum thyroiditis (table 4.9) are important differentials to consider in first trimester and post-partum period respectively.

Beta blockers can be used for symptom control for a brief period. Avoid atenolol during pregnancy.

Graves disease is treated with ATDs (propylthiouracil up to 16th week, carbimazole thereafter) during pregnancy (table 4.8). Aim normal TSH and upper normal FT4 for pregnancy specific ranges. Monitor foetal heart rate and growth, especially if maternal TRAb titres are high.

RAI is absolutely contraindicated. Consider surgery (preferably in second trimester) in ATD failure or intolerance.

Gestational thyrotoxicosis (table 4.7) and post-partum thyroiditis is treated symptomatically with beta blockers

(figure 4.4). Monitor thyroid functions in post-partum thyroiditis for progression to hypothyroidism.

5. THYROID EMERGENCIES

5.1. Myxoedema coma

Myxoedema coma is an endocrine emergency which occurs as the culmination of severe longstanding hypothyroidism or be precipitated by an acute event in a poorly controlled hypothyroidism.

Impaired mental status and hypothermia are hallmark features. Hypotension, bradycardia, hypoventilation, hyponatraemia and hypoglycaemia may occur.

Infection, myocardial infarction, cold exposure, surgery (116) or administration of sedative drugs are potential precipitating factors.

Coexisting adrenal insufficiency either due to autoimmune adrenal disease or hypothalamo-pituitary disease needs to be considered in patients presenting with myxoedema coma, as treatment with levothyroxine will precipitate an acute adrenal insufficiency.

Box 5.1. Management of myxoedema coma

Treatment should be initiated on suspicion without waiting for laboratory confirmation.

- Draw serum for TSH, Free T4 and cortisol.
- Thyroid hormone replacement –
 - Preferably parenteral, due to the aspiration risk and uncertain absorption(117)(20)
 - Initial loading dose of IV LT4 200 - 400 µg followed by daily doses of 50-100 µg IV
 - If T3 is available, an initial loading dose of 5–20 µg can be given, followed by a maintenance dose of 2.5–10 µg every 8 hours (20).
 - If IV LT4 is not available, LT4 can be administered via nasogastric tube. Initial oral loading dose is 500 µg, followed by maintenance dose (117).
 - Whether LT4 or combined T4 and T3 is preferred is unclear due to paucity of data. However combined T4 and T3 may be preferred because of the rapid action and high biological activity of T3 (118)
 - In patients who were on IV LT4, change to an appropriate oral dose of LT4 when the patient can tolerate oral medications. (Oral dose is approximately the intravenous dose divided by 0.75).
- Hydrocortisone 100 mg IV every eight hours until exclusion of possible adrenal insufficiency.
- Supportive measures according to clinical indications:
 - Mechanical ventilation
 - Fluids and vasopressor drugs to correct hypotension
 - Monitoring and correction of electrolytes if indicated
 - Passive rewarming
 - Intravenous dextrose
 - Consider empirical antibiotic treatment
 - Monitor for arrhythmias and treat when indicated

5.2. Thyroid storm

Thyroid storm is a rare disorder with multi-system involvement and high mortality (119).

In the past, the most common precipitating cause was thyroid surgery. Incompletely treated hyperthyroidism or interrupted drug therapy are the leading causes at present (120).

5.2.1. Diagnosis

Thyroid storm is clinical diagnosis and is assisted by Burch–Wartofsky Point Scale (BWPS) (Table 3) or Japanese Thyroid Association (JTA) categories of thyroid storm (120).

If diagnosis is suspected treatment should be commenced immediately to prevent increased risk of mortality.

Table 5.1. Burch–Wartofsky Point Scale for diagnosis of thyrotoxic storm

System involvement	Score determined by severity	Distribution of scores
1. Thermoregulatory dysfunction	5 - 30	99.0-99.9 5 100.0-100.9 10 101.0-101.9- 15 102-102.9 20 103.0-103.9 25 >104 30
2. Central nervous system dysfunction	0 - 30	Absent 0 Mild(agitation) 10 Moderate(delirium,psychosis) 20 Severe(seizure, coma)- 30
3. Cardiovascular dysfunction -Heart rate	5 - 25	100-109- 5 110-119- 10 120-129- 15 130-139- 20 >140- 25
4. Cardiovascular dysfunction -Heart failure	0 - 15	Absent- 0 Mild - 5 Moderate- 10 Severe- 20
5. Cardiovascular dysfunction-Atrial Fibrillation	0 - 10	Absent- 0 Present-10
6. Gastro-intestinal and hepatic dysfunction	0 -20	Absent-0 Moderate-10 Severe(jaundice)-20
7. Precipitant history	0 - 10	Absent-0 Present-10

Adapted from Burch and Wartofsky(119)

A score of 45 or greater is highly suggestive of thyroid storm; a score of 25 to 44 is suggestive of impending storm, and a score below 25 is unlikely to represent thyroid storm.

5.2.2. Management of thyroid storm

Management can be divided into broad areas as outlined below in box 5.2.

Patients who have survived thyroid storm should receive definitive therapy for their underlying hyperthyroidism to avoid any recurrence of this potentially fatal condition (120).

Box 5.2. Management of thyroid storm

1. Ameliorate hyperadrenergic state
 - Propranolol 40-80 mg orally every 6 hours or short acting BBs such as labetalol and esmolol are preferred
 - When BBs are contraindicated, diltiazem can be used for rate control.
 - In high output cardiac failure above agents should be used with caution.
2. Inhibit new TH synthesis
 - Propylthiouracil 500 – 1000 mg load and 200 mg every 4 hours (also and inhibits peripheral conversion of T4 to T3)
3. Inhibition of peripheral conversion of T4 to T3
 - IV hydrocortisone 300 mg load and 100 mg 8 hourly (also corrects relative adrenal insufficiency)
4. Retard the release of pre-formed TH by iodine compounds
 - Saturated solution of potassium iodide (SSKI) 5 drops 6 hourly or Lugol's iodine solution 10 drops 8 hourly
 - Start 1 hour after first ATD dose
5. Deplete TH pool by enhancing clearance through enterohepatic circulation
 - Cholestyramine 4 g in 6 hourly

Other measures

- Consider ICU care
- Peripheral cooling, intra venous fluids and antipyretics
- Plasmapheresis

Note: Salicylates should be avoided as they increase the free TH and also possibly accelerate the metabolic rate.

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