HYPOTHYROIDISM

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- September 2023

To the CHI Hypothyroidism Clinical Guidance-

Issued May 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

CH	Congenital Hypothyroidism
CHI	Council of Health Insurance
CPG	Clinical Practice Guidelines
FT3	Free Triiodothyronine
FT4	Free Thyroxine
Hypo	Hypothyroidism
ICM	Iodine-Based Contrast Media
IDF	CHI Drug Formulary
IRT	Immune Reconstitution Therapy
NBS	Newborn Screening
OHypo	Overt Hypo
PCP	Primary Care Provider
SHypo	Subclinical Hypo
T3	Triiodothyronine
T4	Thyroxine
TA	Thyroid Autoimmunity
TD	Thyroid Dysfunction
TPO-Ab	Anti-Thyroid Peroxidase Antibodies
TRAb	Autoantibodies Against the Thyrotropin Receptor
TRBAb	Thyroid-Stimulating Hormone (TSH) Receptor-Blocking Antibodies
TSH	Thyroid-stimulating hormone

Executive Summary

Hypothyroidism, also referred to as an underactive thyroid, is a medical condition that impacts the thyroid gland, leading to insufficient production of thyroid hormone. This hormone is crucial for regulating metabolism in the body. Individuals with hypothyroidism experience a decrease in the speed of their metabolic system, which gives rise to a range of issues.

Primary hypothyroidism, resulting from thyroid gland damage, or central hypothyroidism, caused by a pituitary gland disorder, can be responsible for the condition. It has the potential to affect various populations, including neonates, children, adults, pregnant women, and the elderly. Hypothyroidism can manifest as either subclinical, with mild or no symptoms, or overt, with noticeable clinical symptoms. In Saudi Arabia, the prevalence of hypothyroidism ranges from 18.7% to 25.5%, with females accounting for 57.5% to 86.3% of cases. Additionally, the occurrence of congenital hypothyroidism among the Saudi population varies from 1 in every 2,666 to 1 in every 4,208 live births.

Typically, the diagnosis of hypothyroidism is based on thyroid function tests due to the non-specific nature of the usual clinical symptoms. Hypothyroidism is identified by a diagnosis of subnormal serum free T4 levels, which can occur in either primary hypothyroidism (characterized by elevated serum TSH levels) or central hypothyroidism (characterized by normal or low serum TSH levels). Levothyroxine (LT4) is the cornerstone for the treatment of hypothyroidism[1].

CHI issued Hypothyroidism 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 Hypothyroidism clinical guidance and seeks to offer guidance for the effective management of Hypothyroidism. It provides an **update on the Hypothyroidism 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 new guidelines that are added to the report** such as: Clinical Practice Recommendations for Assessment and Management of Hypothyroidism **(2022)**, Congenital Hypothyroidism: A **2020–2021** Consensus Guidelines Update— An ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology, **2019** European Thyroid Association Guidelines on the Management of Thyroid Dysfunction following Immune Reconstitution Therapy, **2021** European Thyroid Association Guidelines for the Management of Iodine-Based

Contrast Media-Induced Thyroid Dysfunction, American academy of Pediatrics Congenital Hypothyroidism: Screening and Management **(2023).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it can be concluded that there have been no changes or updates made to any of the previously listed drugs in terms of drug information and prescribing edits since May 2020. Furthermore, now new drugs were added to the SFDA since then.

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 the therapeutic management of hypothyroidism.

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

Table 1. General Recommendations for the Management of Hypothyroidism

Management of Hypothyroidism		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
TSH test is initially ordered for all patients and followed by further evaluation or treatment as needed.	Not graded	Clinical Practice Recommendations for Assessment and Management of Hypothyroidism (2022)[1]
Levothyroxine is the preferred treatment for primary and secondary hypothyroidism in various age groups.	Not graded	Clinical Practice Recommendations for Assessment and Management of Hypothyroidism (2022)[1]
Levothyroxine can also be considered in cases of subclinical hypothyroidism as the initial treatment.	Not graded	Clinical Practice Recommendations for Assessment and Management of Hypothyroidism (2022)[1]

Treatment goals for levothyroxine therapy are to achieve normal TSH levels and alleviate symptoms.	Not graded	Clinical Practice Recommendations for Assessment and Management of Hypothyroidism (2022)[1]
Early detection and management of congenital hypothyroidism (CH) through newborn screening is crucial for preventing neurodevelopmental delays and promoting optimal outcomes.	Level of evidence: 1/+++	European Society for Pediatric Endocrinology and the European Society for Endocrinology Guidelines[2]
Prompt initiation of treatment is recommended if the patient is symptomatic or at high risk (pregnancy, cardiovascular disease), or if thyroid dysfunction persists for more than three months	Level of evidence: 1, øø○○	2019 European Thyroid Association Guidelines3
Starting levothyroxine (LT4) is recommended in patients with overt hypothyroidism	Level of evidence: 1, øø○○	2019 European Thyroid Association Guidelines[3]
A personalized approach to the treatment of ICM-induced Hypo is recommended, considering factors such as clinical symptoms, etiology, and the severity of Hypo, as well as the patient's age, presence of concurrent diseases, and overall clinical condition	Level of evidence: 1, øø○	2021 European Thyroid Association Guidelines4
Newborn screening for CH should be performed on all infants in conjunction with state or provincial public health laboratories.	Not graded	2023 American Academy of Pediatrics[5]
In most cases, treatment involving liothyronine is not recommended. The use of liothyronine in individuals with persistent severe resistance to thyroid hormone elevated TSH levels despite elevated FT4 levels, in whom adequate	Not graded	2023 American Academy of Pediatrics5

control cannot be achieved with L-T4 (levothyroxine) alone, has not been shown to result in improved outcomes. This option should be considered only in consultation with an endocrinologist		
The recommended treatment for congenital hypothyroidism (CH) involves using oral L-T4 at an initial daily dosage ranging from 10 to 15 micrograms per kilogram of body weight	Not graded	2023 American Academy of Pediatrics[5]

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 hypothyroidism report, and the second includes newly added guidelines that have helped generate this report.

1.1 Revised Guidelines

There are no updated versions of the guidelines detailed in the CHI May 2020 report.

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 NICE guidelines of Thyroid disease: assessment and management [2019]	N/A*
1.2 European Thyroid Association (ETA) Guidelines on the Diagnosis and Management of Central Hypothyroidism [2018]	N/A*
1.3 2018 European Thyroid Association (ETA) Guidelines for the Management of Amiodarone-Associated Thyroid Dysfunction	N/A*
1.4 2013 ETA Guideline: Management of Subclinical Hypothyroidism [2013]	N/A*
1.5 Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical	N/A*

Endocrinologists and the American Thyroid Association [2012]	
1.6 Guidelines for the Treatment of Hypothyroidism Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement [2014]	N/A*

*: No updated version available: the existing version is the most recent one and no further updates or revisions have been made or released.

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI hypothyroidism report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
Saudi Society of Endocrinology and Metabolism (SSEM) Clinical Practice Recommendations for Assessment and Management of Hypothyroidism (2022)[1]
Congenital Hypothyroidism: A 2020–2021 Consensus Guidelines Update— An ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology[2]
2019 European Thyroid Association Guidelines on the Management of Thyroid Dysfunction following Immune Reconstitution Therapy[3]
2021 European Thyroid Association Guidelines for the Management of Iodine-Based Contrast Media-Induced Thyroid Dysfunction[4]
American Academy of Pediatrics (AAP) Congenital Hypothyroidism: Screening and Management (2023)[5]

1.2.1 Saudi Society of Endocrinology and Metabolism (SSEM) Clinical Practice Recommendations for Assessment and Management of Hypothyroidism (2022)

The Saudi Society of Endocrinology and Metabolism (SSEM) assembled a panel of experts to develop a consensus that includes the screening, diagnosis, and management of different types of hypothyroidism in different populations, and published its clinical practice recommendations for assessment and management of hypothyroidism in 2022[1]:

- Hypothyroidism, a commonly overlooked but potentially severe disorder, is easily diagnosed through laboratory tests and highly treatable.

- Screening the general population for thyroid disease in asymptomatic nonpregnant adults is not recommended.
- Both the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) suggest measuring TSH levels in individuals at high risk for hypothyroidism, including those with a personal history of type 1 diabetes or other autoimmune diseases, a family history of thyroid disease, a history of neck radiation to the thyroid, or a history of thyroid surgery.
- It is recommended to screen for hypothyroidism in individuals aged 60 years or older and women aged 50 years or older.
- Adults and children with clinical risk factors for hypothyroidism should undergo screening.
- Patients who are considered high-risk for hypothyroidism include those with goiter, a history of autoimmune disease, prior treatment with radioactive iodine or head and neck irradiation, a family history of thyroid disease, current or previous use of medications that can affect thyroid function, clinical suspicion of thyroid disease, type 1 diabetes, new-onset atrial fibrillation, or unexplained anxiety or depression.
- It is recommended to conduct screening for congenital hypothyroidism in all newborns in Saudi Arabia, with special attention given to those at higher risk, such as preterm infants, low birth weight and very low birth weight infants, ill and preterm infants admitted to neonatal intensive care units, and multiple births, especially same-sex twins.
- Avoid routinely measuring thyroid function and/or insulin levels in children with obesity.
- It is recommended to screen for thyroid dysfunction in all asymptomatic pregnant women in the first trimester.
- Screen for thyroid dysfunction in all women who are planning for pregnancy.
- Women with overt hypothyroidism should receive levothyroxine replacement therapy, and the dosage should be adjusted to achieve the target TSH serum level.
- The target TSH level during pregnancy is in the lower half of the trimester-specific reference range. If this is not feasible, the goal is to maintain TSH levels below 2.5 mU/L.
- Pregnant women with TSH levels exceeding 2.5 mU/L should undergo evaluation to determine their TPO-Ab status.

- Serial TSH level assessments should be conducted every 4 to 6 weeks during the first half of pregnancy to adjust levothyroxine dosage and maintain TSH levels within the target range. TSH reassessment is also recommended during the second half of pregnancy.
- In women who are planning pregnancy and are already on levothyroxine therapy, TSH levels should be evaluated prior to conception, and dosage adjustments should be made to achieve a TSH value between the lower reference limit and 2.5 mU/L.
- For women already receiving levothyroxine therapy, the total daily dose should be increased by approximately 25% to 30% during pregnancy.
- TSH (thyroid-stimulating hormone) test should be originally ordered for all patients, and if the results are abnormal, the TSH measurement should be repeated along with further evaluation or treatment as needed. If the TSH level is above the normal range, it is recommended to measure free T4 in the same sample.
- There is no recommendation for routine testing of TPO-Ab (Anti-Thyroid Peroxidase Antibodies).
- For certain patients where thyroiditis is suspected, it is recommended to conduct an initial screening that includes ordering TSH, T4, and anti-TPO tests.
- For newborn screening, it is recommended to use a primary TSH/backup T4 approach, with the TSH sample being collected between 2 to 8 days after birth.
- Do not repeat thyroid function tests if TSH is normal except for diabetes patients.
- In asymptomatic individuals, it is recommended to repeat thyroid function tests if the TSH levels are abnormal. The ideal interval for screening for thyroid dysfunction is between 4 to 8 weeks.
- If symptoms worsen or new symptoms emerge, it is advised to repeat tests for thyroid dysfunction, but not earlier than six weeks from the most recent test.
- Thyroid function tests are primarily used for diagnosing hypothyroidism due to the nonspecific nature of the usual clinical symptoms.
- Primary hypothyroidism is characterized by laboratory findings that involve a reduction in serum free thyroxine (FT4) levels and an elevation in serum thyroid stimulating hormone (TSH) levels.
- In primary hypothyroidism, an increased serum TSH level surpasses the upper limit of the normal reference range, which is typically around 4-5 mU/L. In healthy individuals without thyroid disease, the normal range for serum TSH is usually around 2.5-3 mU/L.

- In adults with TSH levels exceeding the reference range, it is recommended to measure TPO-Abs; however, there is no need to repeat TPO-Abs testing in cases of primary and subclinical hypothyroidism. For children and young individuals with TSH levels above the reference range, it is advisable to conduct TPO-Abs testing, with the possibility of repeating the test during the transition to adult services.
- The diagnosis of central hypothyroidism relies on clinical symptoms and thyroid function tests.
- In secondary (central) hypothyroidism, laboratory findings typically show normal or low levels of TSH along with decreased serum free T4.
- If there is suspicion of pituitary or hypothalamic disease, such as in a young woman with amenorrhea and fatigue, it is advised to measure serum TSH and free T4.
- If a patient exhibits convincing symptoms of hypothyroidism despite having a normal TSH result, it is recommended to measure free T4.
- While measuring T3 is generally not useful in the diagnosis of most patients with suspected central hypothyroidism, it can be considered in cases where the diagnosis is uncertain and may provide some assistance.
- When assessing thyroid function during pregnancy, the typical tests performed are TSH and free T4 measurements.
- In the absence of specific trimester-specific reference ranges, the following general ranges can be used: 0.1-2.5 mU/L for the first trimester, 0.2-3.0 mU/L for the second trimester, and 0.3-3.0 mU/L for the third trimester.
- Whenever possible, it is recommended to establish trimester-specific reference ranges for serum TSH based on local population data that accurately represents the healthcare provider's practice.
- In some cases, measuring total T4 may provide more accurate results compared to free T4 measurements.
- Serum tests for thyroid function are crucial in confirming or ruling out the diagnosis of hypothyroidism.
- Once hypothyroidism is confirmed, additional investigations such as thyroid radionuclide uptake and scan, ultrasonography, thyroglobulin tests, tests for thyroid autoantibodies, or urinary iodine excretion may be conducted to determine the underlying cause.
- In cases of congenital hypothyroidism: elevated TSH levels along with low free T4 levels confirm the diagnosis of primary hypothyroidism; elevated TSH levels along with normal free T4 or total T4 levels indicate subclinical hypothyroidism; and low or normal TSH levels with low free T4 levels suggest the possibility of central hypothyroidism.

- Levothyroxine is the established treatment for addressing primary hypothyroidism in adults, children, and young individuals. This choice is primarily due to its proven effectiveness over the long term, favorable safety profile, ease of administration, and affordability.
- There is no inherent benefit in using levothyroxine (LT4) dissolved in glycerin and provided in gelatin capsules or liquid form compared to tablets. The soft gel capsule or liquid formulation may be considered for patients suspected of having poor absorption of the standard solid tablet. It could also be an option when proton pump inhibitors or coffee are used concurrently or following bariatric surgery. However, increasing the dosage of levothyroxine tablets with TSH monitoring is a more cost-effective approach compared to switching to new formulations.
- We advise patients to continue using the same formulation of levothyroxine that they are currently on.
- It is permissible to use either a generic or a brand-name formulation of levothyroxine. However, if switching between formulations (such as from brand to generic or different brands from different countries) becomes necessary, it should be done cautiously. Following the switch, serum TSH levels should be monitored until they reach a stable state.
- For adults under the age of 65 without a history of cardiovascular disease, the initial dosage of levothyroxine should be 1.6 mcg per kilogram of body weight per day, rounded to the nearest 25 mcg.
- Dosage adjustments should be made based on the individual's actual body weight and ideal body weight.
- Regarding the timing of administration with meals, it is recommended to consistently take levothyroxine either 1 hour before breakfast or at bedtime, after a minimum of 3 hours since the evening meal. This allows for optimal and consistent absorption of the medication.
- The objectives of levothyroxine therapy are to achieve normal levels of serum TSH, alleviate symptoms, and prevent overtreatment.
- When managing primary hypothyroidism using levothyroxine, it is recommended to maintain TSH levels within the normal reference range. The target range for TSH is typically defined as 0.5 to 4.0 mU/L.
- TSH is the recommended marker for monitoring the adequacy of levothyroxine therapy. Free T4, T3, and clinical symptoms should not be used for monitoring and adjusting levothyroxine therapy.

- For adults, TSH levels should be measured every 3 months until they stabilize (two consecutive measurements within the reference range taken three months apart), and then once a year thereafter.
- For children aged 2 years and older and young individuals, Free T4 and TSH levels should be measured every 6-12 weeks until TSH levels stabilize (two consecutive measurements within the reference range taken three months apart). After stabilization, measurements should be taken every 4-6 months until after puberty, and then once a year.
- For children aged between 28 days and 2 years, Free T4 and TSH levels should be measured every 4-8 weeks until TSH levels stabilize (two consecutive measurements within the reference range taken two months apart). During the first year of life, measurements should be taken every 2-3 months, and during the second year of life, measurements should be taken every 3-4 months.
- If there is a weight gain or loss exceeding 10% of body weight, adjustments to levothyroxine doses should be made accordingly.
- When initiating medications such as phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline, it is advisable to measure TSH levels, as higher doses of levothyroxine may be necessary.
- It is important to consider evaluating gastrointestinal disorders like H. pylori-related gastritis, atrophic gastritis, or celiac disease, as the levothyroxine dose requirements in such cases can be higher than anticipated. If these disorders are identified and effectively treated, re-evaluating TSH levels and levothyroxine dosage is recommended.
- If there is ongoing elevation of TSH levels, it is important to assess adherence to therapy, ensure proper administration considering food, other co-medications, or underlying diseases.
- If symptoms persist, adjusting the levothyroxine dose is recommended to achieve optimal well-being without inducing thyrotoxicosis.
- If symptoms persist despite having a normal serum TSH level, it is advisable to measure free T4 along with TSH levels in patients experiencing hypothyroidism symptoms. This helps in excluding other potential causes for the symptoms.
- In patients with cardiovascular disease, the recommended starting dosage of levothyroxine is 12.5 - 25 mcg per day. The dosage should be gradually increased over a period of 4 - 6 weeks, taking into consideration symptoms and serum TSH levels.
- For patients between the ages of 65 and 70, it is recommended to initiate levothyroxine treatment at lower doses ranging from 25 to 50 mcg per day. The

dosage should be adjusted based on TSH levels, particularly for adults with a history of cardiovascular disease.

- Levothyroxine treatment should be initiated as soon as a newborn tests positive in the screening, even before the confirmatory test results are available. In cases where screening tests show borderline results, a treatment decision can be postponed until the confirmatory test results are received.
- Adjusting the levothyroxine dose based on the severity of the initial TSH and T4 deficiency is a sensible approach. For mild cases, a recommended dose of 8 to 10 mcg/kg/day is appropriate. Infants with severe congenital hypothyroidism may require higher doses, ranging from 12.5 to 15 mcg/kg/day.
- The dosing regimen is determined by the age of the child:
    1. Full-term newborns: a dose of 10 to 15 mcg/kg/day
    2. Preterm newborns: a dose of 10 to 15 mcg/kg/day. In milder cases characterized by delayed TSH elevation, a starting dose of 8 to 12 mcg/kg/day is often used.
    3. Ages 1 to 3 years: 4 to 6 mcg/kg of body weight
    4. Ages 3 to 10 years: 3 to 5 mcg/kg
    5. Ages 10 to 16 years: 2 to 4 mcg/kg OR The dosing regimen can be based on body surface area calculated at 100 kg/m^2/day.
- The objective of therapy in infants is to maintain serum TSH levels in the mid-to-upper range of the pediatric reference range and serum thyroxine levels in the mid-to-lower range. The goal is to normalize serum thyroxine levels within approximately 2 to 4 weeks after starting treatment. Once the appropriate dose is determined, monitoring should involve testing serum TSH and FT4 levels every 1 to 2 months during the first year of life, with decreasing frequency as the child grows older. The aim of therapy in children is to normalize their biochemical parameters and reverse the signs and symptoms of hypothyroidism.
- TSH levels should be reassessed 4 to 8 weeks after initiating or discontinuing estrogen therapy, as it may affect levothyroxine requirements. The reassessment interval after starting estrogen therapy is 6 to 12 weeks.
- In hospitalized patients who are unable to take levothyroxine orally, intravenous administration is an option until enteral absorption improves. The intravenous dose should be approximately 70% to 80% of the patient's oral dose. Alternatively, levothyroxine can be administered via nasogastric tube using an extemporaneous preparation or rectally using a hospital-prepared suppository.

- In cases where efforts to enhance adherence to daily oral levothyroxine treatment are unsuccessful, an alternative approach is to administer the total weekly dose of levothyroxine orally (equivalent to 7 times the daily dose).
- When patients show indications of being allergic to levothyroxine, it is advisable to consider various approaches such as modifying the dosage, switching to different formulations or brands of the medication, managing any concurrent iron-deficiency anemia, or seeking consultation with an allergist.
- The regular use of combined T4 and T3 therapy as a treatment for primary hypothyroidism is not recommended.
- When considering the initiation of treatment for subclinical hypothyroidism, it is important to consider certain factors that may indicate underlying thyroid disease. These factors include symptoms of hypothyroidism, a history of radioactive iodine treatment or thyroid surgery, or elevated levels of thyroid autoantibodies.
- Consider initiating levothyroxine treatment for adults diagnosed with subclinical hypothyroidism who have a TSH level of 10 mU/L or higher on two separate occasions spaced three months apart.
- For adults under the age of 65 who have a TSH level above the reference range but below 10 mU/L on two separate occasions three months apart, along with symptoms of hypothyroidism, consider a trial of levothyroxine treatment for a period of six months.
- If symptoms do not improve after starting levothyroxine treatment, re-evaluate the TSH level. If the TSH level remains elevated, adjust the levothyroxine dose accordingly. If symptoms persist even when the serum TSH is within the reference range, consider discontinuing levothyroxine treatment and follow the recommended monitoring guidelines for untreated subclinical hypothyroidism and monitoring after treatment cessation.
- Follow-up and monitoring should be done for patients with primary hypothyroidism.
- In cases of subclinical hypothyroidism in pregnant patients, it is recommended to initiate low-dose levothyroxine treatment. Typically, a dose of 50 mcg/day is sufficient for effective treatment of subclinical hypothyroidism in pregnant women.
- Treatment is generally not recommended when the TSH levels range from 5 to 10 mU/L.
- Levothyroxine replacement therapy may be considered for patients with TSH levels above 10 mU/L who exhibit signs and symptoms consistent with primary

thyroid disease and/or have risk factors associated with disease progression, or in the case of patients aged 2 years and above with:

1. TSH levels equal to or higher than 20 mU/L.
2. TSH levels between 10 and 20 mU/L on two separate occasions spaced three months apart.
3. TSH levels between 5 and 10 mU/L on two separate occasions spaced three months apart, and thyroid dysgenesis, or signs or symptoms of thyroid dysfunction.

- For children aged between 28 days and 2 years, levothyroxine treatment may be initiated if the TSH level is equal to or higher than 10 mU/L. This recommendation is based on the NICE guideline.
- In cases of subclinical hypothyroidism, it is advised to commence levothyroxine treatment at lower doses, typically ranging from 25 to 50 mcg.
- Follow-up and monitoring should be conducted similarly to patients with primary hypothyroidism.
- For adult patients with untreated or stopped treatment for subclinical hypothyroidism, follow-up should be conducted by measuring TSH and free T4 levels once a year if they exhibit features that suggest underlying thyroid disease, such as a history of thyroid surgery or elevated levels of thyroid autoantibodies. If no features suggesting underlying thyroid disease are present, follow-up can be done every 2 to 3 years.
- For untreated children over 2 years old and adolescent patients with subclinical hypothyroidism (TSH < 10 mU/L), follow-up should involve measuring TSH and free T4 levels every 3 to 6 months if they have features indicating underlying thyroid disease, such as thyroid dysgenesis or elevated levels of thyroid autoantibodies. If no features suggesting underlying thyroid disease are present, follow-up can be done every 6 to 12 months.
- For untreated children under 2 years old and adolescent patients with subclinical hypothyroidism (TSH < 10 mU/L), follow-up should involve measuring TSH and free T4 levels every 1 to 3 months.

1.2.2 Congenital Hypothyroidism: A 2020–2021 Consensus Guidelines Update—An ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology

The European Society for Pediatric Endocrinology and the European Society for Endocrinology endorsed a consensus guideline on congenital hypothyroidism

published by the ENDO-European Reference Network Initiative, and the main recommendations are detailed below[2]:

Table 4. Grading Scheme for Recommendations

Grading Scheme for Recommendations	
Grade 1	Strong recommendation (applies to most patients in most circumstances, benefits clearly outweigh the risk)
Grade 2	Weak recommendation (suggested by us or should be considered; the best action may depend on circumstances or patient values, benefits, and risks closely balanced or uncertain)

Table 5. Quality of Evidence

Quality of Evidence	
+00	Low (Case series or nonsystematic clinical observations, inconsistent and unprecise estimates, or with indirect evidence)
++0	Moderate (Studies with methodological flaws, inconsistent or indirect evidence)
+++	High quality (Low risk bias)

- Congenital hypothyroidism (CH) refers to the inadequate production of thyroid hormone (TH) present at birth, resulting in a range of severity in TH deficiency. It can be attributed to abnormalities in the development or function of the thyroid gland, as well as the hypothalamus and pituitary, or impaired TH action.
- Early detection and management of congenital hypothyroidism (CH) using newborn screening plays a crucial role in preventing permanent neurodevelopmental delays and promoting optimal developmental outcomes (1/+++).
- The primary focus of neonatal screening for congenital hypothyroidism (CH) should be on identifying all forms of primary CH, including mild, moderate, and severe cases. The most effective test for detecting primary CH is measuring thyrotropin (TSH) (1/+++).
- Additionally, when financial resources permit, it is recommended to include the measurement of total or free thyroxine (fT4) alongside TSH to screen for central CH (2/+).
- A newborn who receives an abnormal result from neonatal screening should be referred to a specialized center (1/++0).

- Following an abnormal screening result, confirmatory testing should be conducted, which involves measuring serum levels of free thyroxine (fT4) and thyrotropin (TSH) (1/++0).
- If the serum fT4 concentration is below the age-specific reference range and TSH levels are significantly elevated, immediate initiation of levothyroxine (LT4) treatment is recommended (1/+++).
- If the serum concentration of thyrotropin (TSH) is greater than 20 mU/L during confirmatory testing, which typically takes place in the second week of life, treatment should be initiated even if the free thyroxine (fT4) level is within the normal range (based on expert opinion) (2/+00).
- In cases where a healthy neonate has a serum TSH concentration between 6 and 20 mU/L beyond 21 days of age, and the fT4 level falls within the age-specific reference range, we suggest two options: either commence levothyroxine (LT4) treatment immediately and retest the thyroid function after discontinuing treatment at a later stage, or defer treatment and retest after 1 to 2 weeks to reassess the need for intervention (as there is insufficient evidence to support or oppose treatment in this scenario, further investigation is warranted) (2/++0).
- In regions or countries where thyroid function tests are not readily available, initiating LT4 treatment is advised if the filter paper TSH concentration is above 40 mU/L during neonatal screening (based on expert opinion) (2/+00).
- For neonates with central congenital hypothyroidism, it is recommended to initiate LT4 treatment only after confirming intact adrenal function. If coexisting central adrenal insufficiency cannot be ruled out, LT4 treatment must be preceded by glucocorticoid therapy to prevent the potential induction of an adrenal crisis (2/+00).
- For individuals who have recently been diagnosed with congenital hypothyroidism (CH), it is highly recommended to initiate levothyroxine (LT4) treatment before proceeding with thyroid gland imaging studies (1/++0).
- We recommend conducting imaging of the thyroid gland using methods such as radioisotope scanning (scintigraphy) with or without the perchlorate discharge test, ultrasonography (US), or a combination of both (1/++0).

Primary Congenital Hypothyroidism

- Levothyroxine (LT4) is the preferred medication for the treatment of congenital hypothyroidism (CH) (1/++0).
- Levothyroxine (LT4) treatment should be initiated promptly, ideally within the first two weeks after birth or immediately after confirmatory thyroid function testing

in neonates who have been identified with congenital hypothyroidism (CH) through a second routine screening test (1/++0).

- The initial LT4 dose should be determined based on the severity of CH, considering the full spectrum from mild to severe cases (1/++0).
- Infants with severe CH, characterized by very low pre-treatment levels of serum free thyroxine (fT4) (<5 pmol/L) or total T4 along with elevated thyroid-stimulating hormone (TSH) levels beyond the normal range based on age and gestational age (GA), should receive the highest starting dose of LT4 (10-15 µg/kg per day) (1/++0).
- Infants with mild CH (fT4 > 10 pmol/L) and elevated TSH should receive a lower initial dose of LT4 (less than 10 µg/kg per day), and in cases where pre-treatment fT4 levels fall within the age-specific reference range, an even lower starting dose may be considered (between 5 and 10 µg/kg) (1/++0).
- LT4 should be administered orally once daily (1/++0). The evidence regarding brand versus generic LT4 is inconclusive, but based on personal experience and expert opinion, it is recommended to use brand LT4 over generic (2/++0).
- We suggest measuring serum free thyroxine (fT4) and thyroid-stimulating hormone (TSH) concentrations prior to, or at least 4 hours after, the most recent daily administration of levothyroxine (LT4) (1/++0).
- We recommend evaluation of fT4 and TSH according to age-specific reference intervals (1/++0).
- If the thyroid-stimulating hormone (TSH) falls within the age-specific reference range and the free thyroxine (fT4) concentrations are above the upper limit of the reference range, it is acceptable and recommended to maintain the same levothyroxine (LT4) dose (1/++0).
- However, any reduction in the LT4 dose should not be solely based on a single fT4 concentration above the normal range, unless the TSH is suppressed (below the lower limit of the reference range) or there are signs of overtreatment, such as jitteriness or tachycardia (1/++0)
- Unlike adults, in neonates, infants, and children, levothyroxine (LT4) can be administered together with food, if soy protein and vegetable fiber are avoided. It is important to administer LT4 at the same time every day, in relation to food intake. This approach can improve compliance and ensure consistent absorption of LT4, allowing for effective dose titration (2/+00). If there is an unexpected need to increase the LT4 dose or if there is reduced absorption or increased metabolism of thyroxine (T4) due to other diseases, the impact of food or medication should be considered (2/+00). Non-compliance is often the most common cause, especially in teenagers and adolescents.

Central Congenital Hypothyroidism

- In severe forms of central CH (fT4 < 5 pmol/L), we also recommend starting LT4 treatment as soon as possible after birth at doses like in primary CH (10–15 lg/kg per day to normalize ft4 levels rapidly (1/++0).
- In milder forms of central CH, we suggest starting treatment at a lower LT4 dose of 5 to 10 µg/kg per day to avoid the risk of overtreatment (1/++0).
- For newborns with central CH, we recommend monitoring treatment by regularly measuring fT4 and thyrotropin (TSH) levels following the same schedule as in primary CH. The goal is to keep serum fT4 levels above the mean or median value of the age-specific reference interval. If TSH levels are low before treatment, subsequent TSH measurements may not be necessary (1/+00).
- In cases where under- or overtreatment is suspected in patients with central CH, TSH, free triiodothyronine (fT3), or total triiodothyronine (T3) can be measured (1/+00).
- If fT4 levels are around the lower limit of the reference interval, undertreatment should be considered, especially if TSH is above 1.0 mU/L (1/+00).
- On the other hand, if serum fT4 is around or above the upper limit of the reference interval, overtreatment should be considered, particularly if there are clinical signs of thyrotoxicosis or a high fT3 concentration (1/+00).

Diagnostic re-evaluation of thyroid function beyond the first 6 months of life

- When no definitive diagnosis of permanent CH was made in the first weeks or months of life, then reevaluation of the HPT axis after the age of 2 to 3 years is indicated, particularly in children with a gland in situ (GIS), and in those with presumed isolated central CH (1/++0).
- For a precise diagnosis, LT4 treatment should be phased out over a 4 to 6 weeks period or just stopped, and full re-evaluation should be carried out after 4 weeks, consisting of (at least) fT4 and TSH measurement.
- If primary hypothyroidism is confirmed (TSH ‡10 mU/L), consider thyroid imaging and, if possible, genetic testing; if central CH is likely (fT4 below the lower limit of the reference interval in combination with a low normal of only mildly elevated TSH), consider evaluating the other anterior pituitary functions and genetic testing.
- If TSH is above the upper limit of the reference interval but <10 mU/L (primary CH) or fT4 just above the lower limit of the reference interval (central CH), then continue withdrawal and retest in another 3 to 4 weeks (1/++0).

- If a child with no permanent CH diagnosis and a GIS requires a LT4 dose less than 3 lg/kg per day at the age of 6 months, then re-evaluation can be done already at that time (1/++0).
- We recommend avoiding iodine as an antiseptic during peri- and neonatal period, as it can cause transient CH (1/++0).

Treatment and monitoring of pregnant women with CH

- In women with CH who are planning pregnancy, we strongly recommend optimization of LT4 treatment; in addition, these women should be counseled regarding the higher need for LT4 during pregnancy (1/++0).
- fT4 (or total T4) and TSH levels should be monitored every 4 to 6 weeks during pregnancy, aiming at TSH concentrations in accordance with current guidelines on treatment of hypothyroidism during pregnancy, that is, <2.5 mU/L throughout gestation in patients treated with LT4 (1/+00).
- In pregnant women with central CH, the LT4 doses should be increased aiming at an fT4 concentration above the mean/median value of the trimester specific reference interval (1/+00).
- After delivery, we recommend lowering LT4 dose to preconception dose; additional thyroid function testing should be performed at ~6 weeks postpartum (1/++0).
- All pregnant women should ingest ~250 µg iodine per day (1/++0).

1.2.3 2019 European Thyroid Association Guidelines on the Management of Thyroid Dysfunction following Immune Reconstitution Therapy

The following recommendations are retrieved from 2019 European Thyroid Association Guidelines on the Management of Thyroid Dysfunction following Immune Reconstitution Therapy[3]:

Table 6. 2019 European Thyroid Association Guidelines Grading Scheme for Recommendations

Grading Scheme for Recommendations	
Øooo	Very Low
ØØoo	Low
ØØØo	Moderate
ØØØØ	High

Table 7. 2019 European Thyroid Association Guidelines Strengths of Recommendation

Strength of Recommendation	
1	Strong, associated with the phrase “we recommend”
2	Weak, associated with the phrase “we suggest”

- We suggest that before initiating IRT, it is advisable to conduct a thyroid-stimulating hormone (TSH) test on all individuals. In cases where TSH levels are abnormal, it is also recommended to measure free-thyroxine (FT4) and, if possible, free-triiodothyronine (FT3). (1, ⌀⌀○○)
- Thyroid eye disease and cardiac conditions that pose a significant risk in the presence of thyrotoxicosis should be regarded as contraindications to initiating IRT. It is recommended to prioritize the control and treatment of these conditions before considering IRT. (1, ⌀○○○)
- We do not recommend routinely measuring thyroid peroxidase antibodies (TPOAb) or thyrotropin receptor antibodies (TRAb) before initiating IRT. However, it should be noted that the risk of thyroid dysfunction is higher in patients who test positive for thyroid autoantibodies. (2, ⌀⌀○○)
- We do not recommend routine thyroid ultrasound or scintigraphy scans before IRT (1,⌀⌀⌀○)
- To assess for thyroid dysfunction following IRT, it is recommended to perform TSH testing. In addition, depending on the resources available, it may be advisable to routinely measure levels of free-thyroxine (FT4). (1, ⌀⌀⌀○)
- If the initial TSH level falls within the range of 0.10–0.39 mU/L and is low, we recommend repeating the TSH test within one month. (1, ⌀⌀○○)
- We recommend repeat TSH testing within 2 weeks together with FT4 if TSH is elevated, and with FT4 and FT3 if TSH is suppressed (<0.10 mU/L); a full history and examination should also be performed, focusing on thyroid signs, symptoms, and contributing factors (1,⌀⌀⌀○)
- After alemtuzumab treatment, we recommend implementing regular biochemical follow-up by conducting TSH testing every three months. It is crucial not to miss these time points since thyroid dysfunction can develop rapidly. Therefore, efforts should be made to ensure that patients attend their scheduled appointments. (1, ⌀⌀○○)
- It is recommended to instruct individuals undergoing IRT to promptly notify the medical team if they experience signs and symptoms of thyroid dysfunction, such as excessive sweating, unexplained weight loss or gain, nervousness, tachycardia, and increased fatigue. (1, ⌀⌀○○)

- Routine TSH monitoring is not recommended following HAART (Highly Active Antiretroviral Therapy) in HIV patients. However, if clinical grounds raise suspicion of thyroid dysfunction, TSH measurement should be performed. (1, ⌀⌀○○)
- It is suggested to manage the long-term follow-up of patients after bone marrow transplant (BMT) or hematopoietic stem cell transplantation (HSCT) in a specialized setting dedicated to their care. (2, ⌀○○○)
- Routine measurement of thyroid function every three months is recommended and should be continued for a duration of four years following the last alemtuzumab treatment. (1, ⌀⌀○○)
- Once this four-year period is completed, thyroid function testing should be conducted based on the presence of symptoms and signs that indicate potential thyroid dysfunction. (1, ⌀⌀○○)
- During surveillance, it is not recommended to routinely measure thyroid autoantibodies in patients who have normal thyroid function (euthyroid). (1, ⌀⌀○○)
- We suggest that the thyroid function of women pregnant or seeking pregnancy within 4 years of last IRT should be monitored more frequently (i.e., monthly) (2, ⌀○○○)
- According to local resources and services, we suggest that these women should be immediately referred to an endocrinologist as soon as they develop TD, to be commenced on appropriate thyroid treatment and monitoring during pregnancy in a specialist setting. (2, ⌀○○○)
- We recommend to promptly initiate treatment if the patient is symptomatic or at high risk (pregnancy, cardiovascular disease), or if TD persists >3 months (1, ⌀⌀○○)
- In the other cases, we suggest delaying treatment by 3 months to determine if the TD spontaneously resolves, or the thyroid function fluctuates (2, ⌀○○○)
- We recommend starting LT4 in patients with overt hypothyroidism. (1, ⌀⌀○○)

1.2.4 2021 European Thyroid Association Guidelines for the Management of Iodine-Based Contrast Media-Induced Thyroid Dysfunction

The following recommendations are retrieved from 2021 European Thyroid Association Guidelines for the Management of Iodine-Based Contrast Media-Induced Thyroid Dysfunction[4]:

Table 8. 2021 European Thyroid Association Guidelines Grading Scheme for Recommendations

Grading Scheme for Recommendations	
⌀○○○	Very Low
⌀⌀○○	Low
⌀⌀⌀○	Moderate
⌀⌀⌀⌀	High

Table 9. 2021 European Thyroid Association Guidelines Strengths of Recommendation

Strength of Recommendation	
1	Strong recommendation (for or against) because the benefits outweigh the risks and is associated with the phrase "we recommend"
2	Weak recommendation (for or against) in which the treatment depends on the patient's preference because the benefits and risks were uncertain and are associated with the phrase "we suggest."

- Routine baseline thyroid function testing of the general population prior to radiological examinations involving the administration of iodinated contrast media (ICM) is not recommended. (1, ⌀⌀○○)
- Prior to ICM exposure, it is suggested to adopt a comprehensive case-finding approach to identify individuals with undiagnosed thyroid dysfunction. (2, ØØOO)
- In high-risk patients, particularly the elderly and those at risk for cardiovascular diseases, it is recommended to measure baseline serum thyroid-stimulating hormone (TSH) levels as a screening for iodinated contrast media (ICM)-induced thyroid dysfunction. If the TSH level is abnormal, further assessment should include measuring thyroid hormones (T3 and/or T4). (2, ⌀○○○)
- Patients who are receiving thyroid hormone replacement therapy are not susceptible to iodinated contrast media (ICM)-induced thyroid dysfunction and thus do not need any specific management in this regard. (1, ØOOO)
- Routine monitoring of thyroid-stimulating hormone (TSH) levels following the administration of iodinated contrast media (ICM) is not recommended. (1, ØØØO)
- The administration of iodinated contrast media (ICM) can lead to temporary alterations in serum thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3) levels in healthy individuals, typically within the normal

range. When interpreting thyroid function tests, it is advisable to consider recent ICM exposure within the past 1-3 months. (2, ØØØO)

- For patients suspected of iodinated contrast media (ICM)-induced hypothyroidism (Hypo), we recommend performing an initial screening test by measuring serum thyroid-stimulating hormone (TSH) levels. If the TSH level is elevated, further assessment should include measuring serum thyroxine (T4) levels. (1, ØØØØ)
- In cases where the etiology of ICM-induced Hypo is unclear, it is recommended to measure serum thyroid peroxidase antibody (TPO-Ab) levels. (1, ⌀⌀○○)
- For patients newly diagnosed with Hypo, it is suggested to evaluate their history of previous radiological examinations involving ICM within the past 1-2 years, as spontaneous remission may occur over time, potentially avoiding the need for lifelong levothyroxine (LT4) treatment. (2, ⌀○○○)
- A personalized approach to the treatment of iodinated contrast media (ICM)-induced hypothyroidism (Hypo) is recommended, considering factors such as clinical symptoms, etiology, and the severity of Hypo, as well as the patient's age, presence of concurrent diseases, and overall clinical condition. (1, ⌀⌀○○)
- In most cases of ICM-induced Hypo, close monitoring without thyroid hormone replacement is suggested. However, levothyroxine (LT4) treatment may be considered for younger patients experiencing symptoms of Hypo, those with an underlying chronic autoimmune thyroiditis, and women planning pregnancy. (2, ØØOO)
- Close monitoring is advised for elderly patients who develop iodinated contrast media (ICM)-induced subclinical hypothyroidism (SHypo), with a general tendency to avoid levothyroxine treatment. (2, ØØOO)
- It is recommended to closely monitor thyroid function tests in infants who have been exposed to iodinated contrast media (ICM) during maternal or neonatal periods, with particular attention given to premature infants. (2, ØØOO)

1.2.5 American Academy of Pediatrics (AAP) Congenital Hypothyroidism: Screening and Management (2023)

The AAP published its recommendations on the screening and management of congenital hypothyroidism in 2023. They are detailed below[5]:

Newborn Screening

Newborn screening (NBS) for congenital hypothyroidism (CH) should be conducted on every infant, collaborating with state or provincial public health laboratories.

- For the normal newborn infant, obtain the NBS specimen after 24 hours of life (preferably between 48 to 72 hours) and before hospital discharge or 1 week of life, whichever is sooner.
- If the infant is released from the hospital prior to reaching 24 hours of life, collect the NBS sample before their discharge. NBS conducted before 24 hours of life carries a higher chance of producing false-positive outcomes. If necessary, conduct the initial NBS before 48 hours of age, prior to any blood transfusion, if applicable.
- There are three possible strategies for newborn screening (NBS) to detect congenital hypothyroidism (CH). These are detailed in the section regarding NBS Test Strategies in the accompanying technical report:
- The first involves measuring primary TSH followed by reflex thyroxine (T4).
- The second method entails primary T4 measurement with subsequent reflex TSH measurement.
- The third approach combines T4 and TSH measurements.
- In cases where a newborn is transferred to another hospital, the transferring institution should communicate whether the NBS sample has been collected. If it hasn't, the receiving hospital should obtain the NBS specimen following the transfer.
- In situations where any NBS result indicates CH, it's recommended to conduct measurements of serum TSH and free thyroxine (FT4).
- If the first NBS is normal, perform a second NBS at 2 to 4 weeks of age in newborns who:
    1. are acutely ill (admitted to a NICU)
    2. are preterm (< 32 weeks gestation)
    3. have very low birth weight (< 1500 g)
    4. received a transfusion before obtaining the NBS
    5. have a monozygotic twin (or a same-sex twin, if zygosity is not known) or multiple birth
    6. have trisomy 21
- Repeat NBS testing is recommended rather than measurement of serum TSH and FT4 because of the much lower cost of NBS.
- If a second NBS performed before 36 weeks' corrected gestational age is normal, repeat NBS testing is recommended 4 weeks later (6–8 weeks of life) or at 36 weeks' corrected gestational age, whichever is earlier.

- When NBS is performed after 1 week of life, use age-specific reference ranges to interpret results. NBS programs should provide age-specific reference ranges for interpretation.

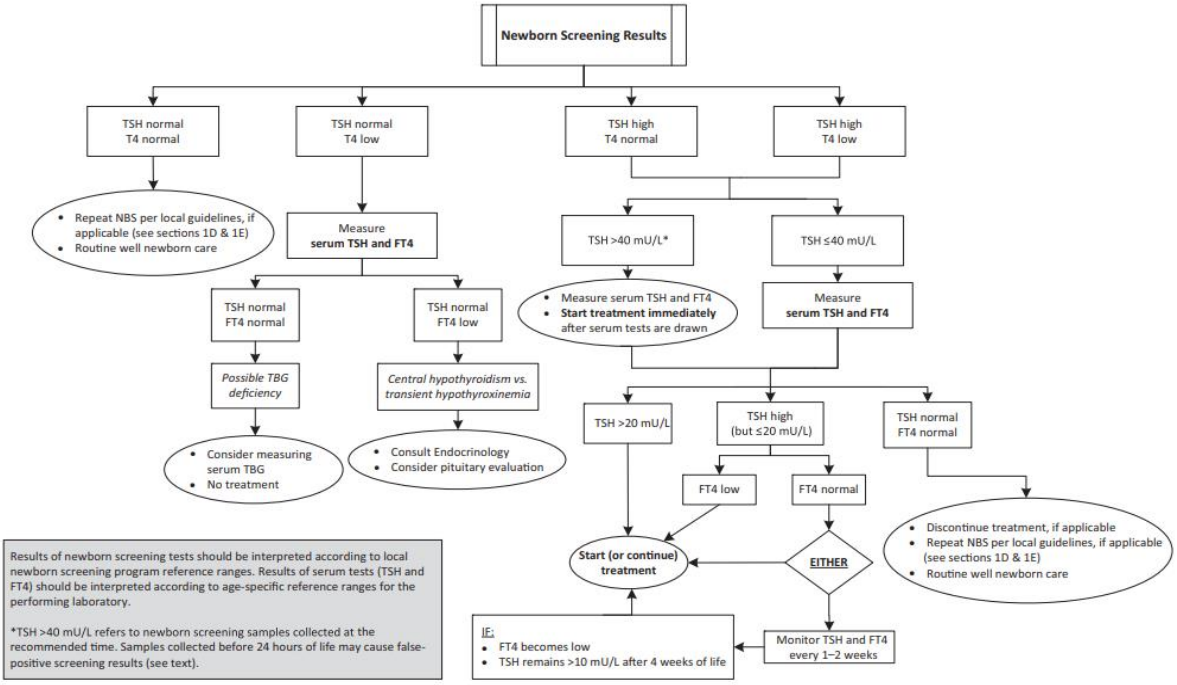

Figure 1. *Algorithm for Action after Newborn Screening for Congenital Hypothyroidism. Adapted from Rose SR, Wassner AJ, Wintergerst KA, et al. CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care Congenital Hypothyroidism: Screening and Management.*

Management of Abnormal NBS

- When the primary care physician (PCP) receives an abnormal NBS result for CH, a confirmatory measurement of TSH and FT4 in a serum sample should be obtained as soon as possible (within 24 hours, when possible).
- Consultation with a pediatric endocrinologist is indicated, if possible, to assist in diagnosis and management.
- Immediate follow-up actions are based on the TSH level of the NBS:
    1. If the NBS TSH is >40 mIU/L, L-T4 treatment should be initiated after drawing the confirmatory serum sample, without waiting for the results.
    2. If the NBS TSH is ≤40 mIU/L, await the results of the confirmatory serum sample (preferably with a 24-hour turnaround time), and hold off on starting L-T4 treatment.

- The infant should be evaluated by a physician (PCP or pediatric endocrinologist) without delay, optimally within 24 hours or on the next office day after the NBS results are received. The physician should:
    1. Obtain a complete history that includes prenatal maternal thyroid status, maternal medications, and family history.
    2. Perform a complete physical examination.
    3. Assess the risk of Thyroid-stimulating hormone (TSH) receptor-blocking antibodies (TRBAb) mediated hypothyroidism and consider measuring TRBAb in the infant and/or mother if there is a history of a maternal autoimmune thyroid disorder or a previous infant affected by maternal TRBAb. If TRBAb are present, no specific additional treatment is needed besides management of the hypothyroidism, and a transient course may be anticipated.
    4. Consider obtaining imaging to establish the etiology of CH but only if the results will influence clinical management.
- The subsequent steps depend on the results of the confirmatory serum sample:
    1. If serum TSH is high and serum FT4 is low, initiate or continue L-T4 treatment.
    2. If serum TSH is greater than 20 mIU/L and serum FT4 is within the normal range, start or continue L-T4 treatment.
    3. If serum TSH is elevated but less than or equal to 20 mIU/L and serum FT4 is within the normal range, you may consider initiating L-T4 treatment. Alternatively, closely monitor serum TSH and FT4 every 1 to 2 weeks without treatment. If FT4 decreases or elevated TSH persists beyond 4 weeks of age, it's recommended to start L-T4 treatment.
    4. For infants with serum TSH elevation between 5 and 10 mIU/L that continues beyond 4 weeks of age, there isn't enough evidence to suggest treatment or observation. In such cases, it's advised to consult a pediatric endocrinologist to develop a patient-specific management plan if that hasn't already occurred.
    5. If serum TSH is within the normal or low range and serum FT4 is low, consider evaluating for possible central hypothyroidism with further testing as needed. Conduct confirmatory serum testing including TSH with FT4. Measuring thyroxine-binding globulin concentration when T4 is low but FT4 is normal might help differentiate central hypothyroidism from thyroxine-binding globulin deficiency. Infants with central CH should be assessed by a pediatric endocrinologist for additional hypothalamic-pituitary dysfunction in consultation.

Consideration should be given to the timing of this evaluation before starting L-T4 treatment, because such treatment may lower cortisol levels.

Imaging

- Thyroid imaging is not obligatory when assessing infants with CH and can be considered if it would impact clinical decisions. The choice to proceed with imaging can be guided by consulting a pediatric endocrinologist.
- Efforts to conduct imaging should never cause a delay in the treatment of CH.
- Thyroid ultrasonography or scintigraphy as imaging methods might help determine the cause of CH in some cases. Nevertheless, in many situations, imaging does not modify the clinical management of the patient before the age of 3 years.

Treatment of CH

- The recommended treatment for congenital hypothyroidism (CH) involves using oral L-T4 at an initial daily dosage ranging from 10 to 15 micrograms per kilogram of body weight.
- Treatment should be initiated as soon as possible after the diagnosis is confirmed (optimally by 2 weeks of age if identified on the first NBS)
- Downward adjustment of the dose after laboratory evaluation at 2 weeks of age may be needed to avoid overtreatment.
- Enteral administration of L-T4 tablets is the treatment of choice. L-T4 tablets can be crushed and suspended by the parent or guardian in 2 to 5 mL (~ 1 tsp) of human milk, nonsoy-containing formula, or water.
    - A commercial oral solution of L-T4 is approved by the US Food and Drug Administration for use in children; however, limited experience with its use showed that dosing may differ slightly from dosing with tablet formulations.29,30 L-T4 suspensions prepared by compounding pharmacies may lead to unreliable dosing.
- L-T4 can be given at any point during the day to infants and young children, whether in the morning or evening, with or without feeding, as long as the timing and method of administration remain constant. The presence of soy, fiber, iron, or calcium during administration can hinder L-T4 absorption. Breastfeeding can continue without disruption. In instances where oral administration isn't feasible, intravenous L-T4 can be given at 75% of the enteral dose.

- The aim of administering L-T4 is to facilitate typical neurocognitive development and growth. Attaining the best possible results hinges on promptly starting appropriate L-T4 treatment, ideally within the first two weeks of life when identified through the initial newborn screening (NBS), especially in instances of severe CH.
- Once the initial normalization is achieved, serum TSH levels should be kept within the reference range appropriate for the individual's age. Additionally, serum FT4 levels should be maintained in the upper half of the age-specific reference range, unless maintaining a serum FT4 level within this range would lead to a TSH level falling below the reference range.
- Ideally, the same L-T4 formulation should be maintained consistently until 3 years of age to achieve consistent euthyroidism and minimize the need for additional laboratory monitoring. If feasible, the use of a brand name L-T4 formulation to provide a consistent formulation may be superior for children with severe CH.43 If generic L-T4 is prescribed, it is preferable to use L-T4 from a consistent manufacturer.
- Using liothyronine treatment is typically not recommended. The application of liothyronine in individuals with ongoing severe resistance to thyroid hormone (elevated TSH despite elevated FT4), who can't achieve sufficient control through L-T4 alone, hasn't been shown to enhance outcomes. This option should only be contemplated under the guidance of a pediatric endocrinologist.

Table 10. Treatment and Monitoring of Congenital Hypothyroidism. Adapted from Rose SR, Wassner AJ, Wintergerst KA, et al. CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care Congenital Hypothyroidism: Screening and Management.

Treatment with levothyroxine
Administer daily at a consistent time and in a consistent manner
Preferred: enteral route
Preferred: tablets, crush and suspend in 2–5 mL of human milk, non-soy-containing formula, or water
Alternative: commercial branded oral solution
Administer with or without food
Alternative route: intravenous route
75% of enteral dosing
Laboratory monitoring
Preferred: TSH and FT4
Alternative: TSH and Total T4
Therapeutic targets:
TSH:[a] age-specific reference range (generally 0.5–5 mIU/L after 3 mo of life)
FT4 (or total T4): upper half of age-specific reference range

[a] For central hypothyroidism, measure only FT4 (or total T4).

Monitoring

- Throughout the initial three years of life, consistent clinical assessment should be carried out as outlined below. This assessment involves evaluating developmental advancements and growth, as detailed in the Monitoring section of the accompanying technical report.
- Due to the heightened likelihood of hearing impairments in those with CH, a formal hearing evaluation should be contemplated whenever clinical indications of hearing issues or atypical language development arise.
- Serum TSH and FT4 should be measured:
    1. One to 2 weeks after the initiation of L-T4 treatment and every 2 weeks until serum TSH level is normal.
    2. Every 1 to 2 months during the first 6 months of life (monthly in infants with severe CH [initial serum TSH >100 mIU/L or FT4 < 0.4 ng/dL])
    3. Every 2 to 3 months during the second 6 months of life; and
    4. Every 3 to 4 months between 1 and 3 years of age.

Long-Term Follow-Up

After 3 years of age, measurement of TSH is recommended:

1. Every 6 to 12 months until growth is complete
2. Four to six weeks after any change in LT-4 dose or formulation
3. At more frequent intervals in children with severe CH, problems with adherence to the L-T4 treatment plan, or TSH levels outside the age-specific reference range. D. After 3 years of age, monitoring of TSH is sufficient. FT4 may be measured if medication adherence or suboptimal control is a concern. E. After the first 3 years of life, clinical evaluation and assessment of growth and development should be performed every 6 to 12 months.

Assessment of the Permanence of Hypothyroidism

- Permanent congenital hypothyroidism (CH) is verified in situations involving thyroid dysgenesis or if the serum TSH rises above 10 mIU/L after the initial year of life.
- Lifelong L-T4 therapy. Is required for patients with permanent CH.
- If a definitive diagnosis of permanent congenital hypothyroidism (CH) hasn't been established, it's advisable to seriously contemplate discontinuing L-T4 therapy when the child reaches 3 years of age, especially if they are effectively

managed with a low L-T4 dosage (<2 mcg/kg/day). A trial off L-T4 may be conducted as follows:

1. Discontinue L-T4 for 4 weeks, then measure serum TSH and FT4 levels.
2. If TSH and FT4 levels remain in the age-specific reference range, transient CH is confirmed.
3. If the TSH is >10 mIU/L and/ or FT4 is low, permanent CH is confirmed and LT-4 therapy should be reinstituted.
4. If the TSH is mildly elevated (greater than the age-specific reference range, but ≤10 mIU/L) and FT4 is normal, repeat serum TSH and FT4 levels in another 4 to 8 weeks to determine if there is (1) normal thyroid function (indicating transient CH), (2) permanent CH (TSH >10 mIU/L or low FT4), or (3) persistent hyperthyrotropinemia (TSH persistently elevated but ≤ 10 mIU/L, with normal FT4). There is insufficient evidence to determine if the treatment of persistent hyperthyrotropinemia is of clinical benefit, but many practitioners elect to treat it out of caution.
5. It is critical that patients not be lost to follow-up while trialing off L-T4 therapy.

Section 2.0 Drug Therapy in Hypothyroidism

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1. Additions

After May 2020, there have been no hypothyroidism drugs that have received Saudi FDA approval.

2.2. Modifications

No modifications have been made since May 2020.

2.3. Delisting

No drugs were delisted from SFDA.

Section 3.0 Key Recommendations Synthesis

- Hypothyroidism is easily diagnosed through laboratory tests and highly treatable[1].
- General population screening for thyroid disease is not recommended, but certain groups should be screened[1].
- High-risk individuals for hypothyroidism include those with goiter, autoimmune disease history, prior treatments affecting thyroid function, family history of thyroid disease, and more[1].
- Newborns in Saudi Arabia should be screened for congenital hypothyroidism, with special attention given to high-risk infants[1].
- Screening for thyroid dysfunction is recommended in pregnant women and those planning for pregnancy[1].
- TSH is the screening test of choice for all patients. It is followed by further evaluation or treatment as needed. Thyroid function tests are essential for diagnosing and monitoring hypothyroidism[1].
- Levothyroxine is the preferred treatment for primary and subclinical hypothyroidism in various age groups[1].
- Treatment goals for levothyroxine therapy are to achieve normal TSH levels and alleviate symptoms[1].
- Early detection and management of congenital hypothyroidism (CH) through newborn screening is crucial for preventing neurodevelopmental delays and promoting optimal outcomes. (Level of evidence: 1/+++)[2].
- Immediate initiation of levothyroxine (LT4) treatment is recommended if fT4 levels are below the reference range and TSH levels are significantly elevated. (Level of evidence: 1/+++)[2].
- Before initiating IRT (immune reconstitution therapy), it is advisable to conduct a TSH test on all individuals. In cases where TSH levels are abnormal, it is also recommended to measure FT4 and, if possible, FT3. (Level of evidence: 1, øø○○)[3].
- Routine measurement of thyroid peroxidase antibodies (TPOAb) or thyrotropin receptor antibodies (TRAb) before initiating IRT is not recommended. However, the risk of thyroid dysfunction is higher in patients who test positive for thyroid autoantibodies. (Level of evidence: 2, øø○○)[3].
- To assess for thyroid dysfunction following IRT, it is recommended to perform TSH testing. In addition, depending on the resources available, it may be advisable to routinely measure levels of FT4. (Level of evidence: 1, øøø○)[3].

- After alemtuzumab treatment, we recommend implementing regular biochemical follow-up by conducting TSH testing every three months. It is crucial not to miss these time points since thyroid dysfunction can develop rapidly. Therefore, efforts should be made to ensure that patients attend their scheduled appointments. (Level of evidence: 1, ⌀⌀○○)[3].
- Prompt initiation of treatment is recommended if the patient is symptomatic or at high risk (pregnancy, cardiovascular disease), or if thyroid dysfunction persists for more than three months. (Level of evidence: 1, ⌀⌀○○)[3].
- In other cases, delaying treatment by three months to determine if thyroid dysfunction spontaneously resolves or fluctuates is suggested. (Level of evidence: 2, ⌀○○○)[3].
- Starting levothyroxine (LT4) is recommended in patients with overt hypothyroidism. (Level of evidence: 1, ⌀⌀○○)[3].
- Patients who are receiving thyroid hormone replacement therapy are not susceptible to ICM-induced thyroid dysfunction and thus do not need any specific management in this regard. (Level of evidence: 1, ØOOO)[3].
- For patients suspected of ICM-induced hypothyroidism (Hypo), an initial screening test by measuring serum thyroid-stimulating hormone (TSH) levels is recommended. If the TSH level is elevated, further assessment should include measuring serum thyroxine (T4) levels. (Level of evidence: 1, ØØØØ)[4].
- For patients newly diagnosed with Hypo, evaluating their history of previous radiological examinations involving ICM within the past 1-2 years is suggested, as spontaneous remission may occur over time, potentially avoiding the need for lifelong levothyroxine (LT4) treatment. (Level of evidence: 2, ⌀○○○)[4].
- A personalized approach to the treatment of ICM-induced Hypo is recommended, considering factors such as clinical symptoms, etiology, and the severity of Hypo, as well as the patient's age, presence of concurrent diseases, and overall clinical condition. (Level of evidence: 1, ⌀⌀○○)[4].
- In most cases of ICM-induced Hypo, close monitoring without thyroid hormone replacement is suggested. However, LT4 treatment may be considered for younger patients experiencing symptoms of Hypo, those with underlying chronic autoimmune thyroiditis, and women planning pregnancy. (Level of evidence: 2, ØØOO)[4].
- The recommended treatment for congenital hypothyroidism (CH) involves using oral L-T4 at an initial daily dosage ranging from 10 to 15 micrograms per kilogram of body weight[5].

- Typically, the use of liothyronine treatment is not advised. Administering liothyronine to individuals with persistent severe resistance to thyroid hormone (characterized by elevated TSH levels despite elevated FT4), who aren't able to achieve adequate control through L-T4 alone, has not demonstrated improved outcomes. This choice should only be considered with the counsel of a pediatric endocrinologist[5].
- Newborn screening (NBS) for congenital hypothyroidism (CH) should be conducted on every infant, collaborating with state or provincial public health laboratories[5].
- Thyroid imaging is not obligatory when assessing infants with CH and can be considered if it would impact clinical decisions. The choice to proceed with imaging can be guided by consulting a pediatric endocrinologist[5].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Hypothyroidism report** and aims to provide recommendations to aid in the management of Hypothyroidism. 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 Hypothyroidism. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

1. Alsifri S, Aljuhani N, Aljedai A, et al. Clinical Practice Recommendations for Assessment and Management of Hypothyroidism. *Int J Clin Med*. 2022;13(12):650-678. doi:10.4236/ijcm.2022.1312046

2. Van Trotsenburg P, Stoupa A, Léger J, et al. Congenital Hypothyroidism: A 2020-2021 Consensus Guidelines Update - An ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. *Thyroid*. 2021;31(3):387-419. doi:10.1089/thy.2020.0333

3. Muller I, Moran C, Lecumberri B, et al. 2019 European Thyroid Association Guidelines on the Management of Thyroid Dysfunction following Immune Reconstitution Therapy. *Eur Thyroid J*. 2019;8(4):173-185. doi:10.1159/000500881

4. Bednarczuk T, Brix TH, Schima W, Zettinig G, Kahaly GJ. 2021 European Thyroid Association Guidelines for the Management of Iodine-Based Contrast Media-Induced Thyroid Dysfunction. *Eur Thyroid J*. 2021;10(4):269-284. doi:10.1159/000517175

5. Rose SR, Wassner AJ, Wintergerst KA, et al. *CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care Congenital Hypothyroidism: Screening and Management*. http://publications.aap.org/pediatrics/article-pdf/151/1/e2022060419/1449605/peds_2022060419.pdf

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. Hypothyroidism Scope

Missing Guidelines	Rationale/Updates
Clinical Practice Recommendations for Assessment and Management of Hypothyroidism (2022)[1]	• Hypothyroidism, a commonly overlooked but potentially severe disorder, is easily diagnosed through laboratory tests and highly treatable. • Screening the general population for thyroid disease in asymptomatic nonpregnant adults is not recommended. • It is recommended to screen for hypothyroidism in individuals aged 60 years or older and women aged 50 years or older. • Adults and children with clinical risk factors for hypothyroidism should undergo screening. • Patients who are considered high-risk for hypothyroidism include those with goiter, a history of autoimmune disease, prior treatment with radioactive iodine or head and neck irradiation, a family history of thyroid disease, current or previous use of medications that can affect thyroid function, clinical suspicion of thyroid disease, type 1 diabetes, new-onset atrial fibrillation, or unexplained anxiety or depression. • It is recommended to conduct screening for congenital hypothyroidism in all newborns in Saudi Arabia, with special attention given to those at higher risk, such as preterm infants, low birth weight and very low birth weight infants, ill and preterm infants admitted to neonatal intensive care units, and multiple births, especially same-sex twins. • Avoid routinely measuring thyroid function and/or insulin levels in children with obesity. • It is recommended to screen for thyroid dysfunction in all asymptomatic pregnant women in the first trimester. • Screen for thyroid dysfunction in all women who are planning for pregnancy. • TSH (thyroid-stimulating hormone) test should be originally ordered for all patients, and if the results are abnormal, the TSH measurement should be repeated along with further evaluation or treatment as needed. If the TSH level is above the normal range, it is recommended to measure free T4 in the same sample. • There is no recommendation for routine testing of TPO-Ab (Anti-Thyroid Peroxidase Antibodies). Both the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) suggest measuring TSH levels in individuals at high risk for hypothyroidism, including those with a personal history of

	type 1 diabetes or other autoimmune diseases, a family history of thyroid disease, a history of neck radiation to the thyroid, or a history of thyroid surgery. • For certain patients where thyroiditis is suspected, it is recommended to conduct an initial screening that includes ordering TSH, T4, and anti-TPO tests. • For newborn screening, it is recommended to use a primary TSH/backup T4 approach, with the TSH sample being collected between 2 to 8 days after birth. • Do not repeat thyroid function tests if TSH is normal except for diabetes patients. • In asymptomatic individuals, it is recommended to repeat thyroid function tests if the TSH levels are abnormal. The ideal interval for screening for thyroid dysfunction is between 4 to 8 weeks. • If symptoms worsen or new symptoms emerge, it is advised to repeat tests for thyroid dysfunction, but not earlier than six weeks from the most recent test. • Thyroid function tests are primarily used for diagnosing hypothyroidism due to the nonspecific nature of the usual clinical symptoms. • Primary hypothyroidism is characterized by laboratory findings that involve a reduction in serum free thyroxine (FT4) levels and an elevation in serum thyroid stimulating hormone (TSH) levels. • In primary hypothyroidism, an increased serum TSH level surpasses the upper limit of the normal reference range, which is typically around 4-5 mU/L. In healthy individuals without thyroid disease, the normal range for serum TSH is usually around 2.5-3 mU/L. • In adults with TSH levels exceeding the reference range, it is recommended to measure TPO-Abs; however, there is no need to repeat TPO-Abs testing in cases of primary and subclinical hypothyroidism. For children and young individuals with TSH levels above the reference range, it is advisable to conduct TPO-Abs testing, with the possibility of repeating the test during the transition to adult services. • The diagnosis of central hypothyroidism relies on clinical symptoms and thyroid function tests. • In secondary (central) hypothyroidism, laboratory findings typically show normal or low levels of TSH along with decreased serum free T4. • If there is suspicion of pituitary or hypothalamic disease, such as in a young woman with amenorrhea and fatigue, it is advised to measure serum TSH and free T4.

	• If a patient exhibits convincing symptoms of hypothyroidism despite having a normal TSH result, it is recommended to measure free T4. • While measuring T3 is generally not useful in the diagnosis of most patients with suspected central hypothyroidism, it can be considered in cases where the diagnosis is uncertain and may provide some assistance. • Overt hypothyroidism is characterized by an elevated TSH level accompanied by a decreased free T4 level, which varies depending on the population and trimester. • In the absence of specific trimester-specific reference ranges, the following general ranges can be used: 0.1-2.5 mU/L for the first trimester, 0.2-3.0 mU/L for the second trimester, and 0.3-3.0 mU/L for the third trimester. • Whenever possible, it is recommended to establish trimester-specific reference ranges for serum TSH based on local population data that accurately represents the healthcare provider's practice. • When assessing thyroid function during pregnancy, the typical tests performed are TSH and free T4 measurements. • In some cases, measuring total T4 may provide more accurate results compared to free T4 measurements. • Serum tests for thyroid function are crucial in confirming or ruling out the diagnosis of hypothyroidism. • Once hypothyroidism is confirmed, additional investigations such as thyroid radionuclide uptake and scan, ultrasonography, thyroglobulin tests, tests for thyroid autoantibodies, or urinary iodine excretion may be conducted to determine the underlying cause. • In cases of congenital hypothyroidism: elevated TSH levels along with low free T4 levels confirm the diagnosis of primary hypothyroidism; elevated TSH levels along with normal free T4 or total T4 levels indicate subclinical hypothyroidism; and low or normal TSH levels with low free T4 levels suggest the possibility of central hypothyroidism. • If hypothyroidism is confirmed, additional investigations such as thyroid radionuclide uptake and scan, ultrasonography, serum thyroglobulin, tests for thyroid autoantibodies, or urinary iodine excretion may be conducted to determine the underlying cause. • Regarding congenital hypothyroidism, Recommendation 34 states that a diagnosis of primary hypothyroidism is confirmed when there are elevated TSH levels along with low free T4 levels. Subclinical hypothyroidism is defined by elevated TSH levels along with normal free T4 or total

	T4 levels. The possibility of central hypothyroidism is suggested when TSH levels are low or normal along with low free T4 levels. • Levothyroxine is the established treatment for addressing primary hypothyroidism in adults, children, and young individuals. This choice is primarily due to its proven effectiveness over the long term, favorable safety profile, ease of administration, and affordability. • There is no inherent benefit in using levothyroxine (LT4) dissolved in glycerin and provided in gelatin capsules or liquid form compared to tablets. The soft gel capsule or liquid formulation may be considered for patients suspected of having poor absorption of the standard solid tablet. It could also be an option when proton pump inhibitors or coffee are used concurrently or following bariatric surgery. However, increasing the dosage of levothyroxine tablets with TSH monitoring is a more cost-effective approach compared to switching to new formulations. • We advise patients to continue using the same formulation of levothyroxine that they are currently on. • It is permissible to use either a generic or a brand-name formulation of levothyroxine. However, if switching between formulations (such as from brand to generic or different brands from different countries) becomes necessary, it should be done cautiously. Following the switch, serum TSH levels should be monitored until they reach a stable state. • For adults under the age of 65 without a history of cardiovascular disease, the initial dosage of levothyroxine should be 1.6 mcg per kilogram of body weight per day, rounded to the nearest 25 mcg. • Dosage adjustments should be made based on the individual's actual body weight and ideal body weight. • Regarding the timing of administration with meals, it is recommended to consistently take levothyroxine either 1 hour before breakfast or at bedtime, after a minimum of 3 hours since the evening meal. This allows for optimal and consistent absorption of the medication. • The objectives of levothyroxine therapy are to achieve normal levels of serum TSH, alleviate symptoms, and prevent overtreatment. • When managing primary hypothyroidism using levothyroxine, it is recommended to maintain TSH levels within the normal reference range. The target range for TSH is typically defined as 0.5 to 4.0 mU/L.

	• TSH is the recommended marker for monitoring the adequacy of levothyroxine therapy. Free T4, T3, and clinical symptoms should not be used for monitoring and adjusting levothyroxine therapy. • For adults, TSH levels should be measured every 3 months until they stabilize (two consecutive measurements within the reference range taken three months apart), and then once a year thereafter. • For children aged 2 years and older and young individuals, Free T4 and TSH levels should be measured every 6-12 weeks until TSH levels stabilize (two consecutive measurements within the reference range taken three months apart). After stabilization, measurements should be taken every 4-6 months until after puberty, and then once a year. • For children aged between 28 days and 2 years, Free T4 and TSH levels should be measured every 4-8 weeks until TSH levels stabilize (two consecutive measurements within the reference range taken two months apart). During the first year of life, measurements should be taken every 2-3 months, and during the second year of life, measurements should be taken every 3-4 months. • If there is a weight gain or loss exceeding 10% of body weight, adjustments to levothyroxine doses should be made accordingly. • When initiating medications such as phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline, it is advisable to measure TSH levels, as higher doses of levothyroxine may be necessary. • It is important to consider evaluating gastrointestinal disorders like H. pylori-related gastritis, atrophic gastritis, or celiac disease, as the levothyroxine dose requirements in such cases can be higher than anticipated. If these disorders are identified and effectively treated, re-evaluating TSH levels and levothyroxine dosage is recommended. • If there is ongoing elevation of TSH levels, it is important to assess adherence to therapy, ensure proper administration considering food, other co-medications, or underlying diseases. • If symptoms persist, adjusting the levothyroxine dose is recommended to achieve optimal well-being without inducing thyrotoxicosis. • If symptoms persist despite having a normal serum TSH level, it is advisable to measure free T4 along with TSH levels in patients experiencing hypothyroidism

	symptoms. This helps in excluding other potential causes for the symptoms. • In patients with cardiovascular disease, the recommended starting dosage of levothyroxine is 12.5 - 25 mcg per day. The dosage should be gradually increased over a period of 4 - 6 weeks, taking into consideration symptoms and serum TSH levels. • For patients between the ages of 65 and 70, it is recommended to initiate levothyroxine treatment at lower doses ranging from 25 to 50 mcg per day. The dosage should be adjusted based on TSH levels, particularly for adults with a history of cardiovascular disease. • Levothyroxine treatment should be initiated as soon as a newborn tests positive in the screening, even before the confirmatory test results are available. In cases where screening tests show borderline results, a treatment decision can be postponed until the confirmatory test results are received. • Adjusting the levothyroxine dose based on the severity of the initial TSH and T4 deficiency is a sensible approach. For mild cases, a recommended dose of 8 to 10 mcg/kg/day is appropriate. Infants with severe congenital hypothyroidism may require higher doses, ranging from 12.5 to 15 mcg/kg/day. • The dosing regimen is determined by the age of the child: • Full-term newborns: a dose of 10 to 15 mcg/kg/day • Preterm newborns: a dose of 10 to 15 mcg/kg/day. In milder cases characterized by delayed TSH elevation, a starting dose of 8 to 12 mcg/kg/day is often used. • Ages 1 to 3 years: 4 to 6 mcg/kg of body weight • Ages 3 to 10 years: 3 to 5 mcg/kg • Ages 10 to 16 years: 2 to 4 mcg/kg OR The dosing regimen can be based on body surface area calculated at 100 kg/m^2/day. • The objective of therapy in infants is to maintain serum TSH levels in the mid-to-upper range of the pediatric reference range and serum thyroxine levels in the mid-to-lower range. The goal is to normalize serum thyroxine levels within approximately 2 to 4 weeks after starting treatment. Once the appropriate dose is determined, monitoring should involve testing serum TSH and FT4 levels every 1 to 2 months during the first year of life, with decreasing frequency as the child grows older. The aim of therapy in children is to normalize their biochemical parameters and reverse the signs and symptoms of hypothyroidism.

	• Women with overt hypothyroidism should receive levothyroxine replacement therapy, and the dosage should be adjusted to achieve the target TSH serum level. • The target TSH level during pregnancy is in the lower half of the trimester-specific reference range. If this is not feasible, the goal is to maintain TSH levels below 2.5 mU/L. • Serial TSH level assessments should be conducted every 4 to 6 weeks during the first half of pregnancy to adjust levothyroxine dosage and maintain TSH levels within the target range. TSH reassessment is also recommended during the second half of pregnancy. • In women who are planning pregnancy and are already on levothyroxine therapy, TSH levels should be evaluated prior to conception, and dosage adjustments should be made to achieve a TSH value between the lower reference limit and 2.5 mU/L. • For women already receiving levothyroxine therapy, the total daily dose should be increased by approximately 25% to 30% during pregnancy. • TSH levels should be reassessed 4 to 8 weeks after initiating or discontinuing estrogen therapy, as it may affect levothyroxine requirements. The reassessment interval after starting estrogen therapy is 6 to 12 weeks. • In hospitalized patients who are unable to take levothyroxine orally, intravenous administration is an option until enteral absorption improves. The intravenous dose should be approximately 70% to 80% of the patient's oral dose. Alternatively, levothyroxine can be administered via nasogastric tube using an extemporaneous preparation or rectally using a hospital-prepared suppository. • In cases where efforts to enhance adherence to daily oral levothyroxine treatment are unsuccessful, an alternative approach is to administer the total weekly dose of levothyroxine orally (equivalent to 7 times the daily dose). • When patients show indications of being allergic to levothyroxine, it is advisable to consider various approaches such as modifying the dosage, switching to different formulations or brands of the medication, managing any concurrent iron-deficiency anemia, or seeking consultation with an allergist. • We do not recommend the regular use of combined T4 and T3 therapy as a treatment for primary hypothyroidism. • When considering the initiation of treatment for subclinical hypothyroidism, it is important to consider certain factors that may indicate underlying thyroid

	disease. These factors include symptoms of hypothyroidism, a history of radioactive iodine treatment or thyroid surgery, or elevated levels of thyroid autoantibodies. • Consider initiating levothyroxine treatment for adults diagnosed with subclinical hypothyroidism who have a TSH level of 10 mU/L or higher on two separate occasions spaced three months apart. • For adults under the age of 65 who have a TSH level above the reference range but below 10 mU/L on two separate occasions three months apart, along with symptoms of hypothyroidism, consider a trial of levothyroxine treatment for a period of six months. • If symptoms do not improve after starting levothyroxine treatment, re-evaluate the TSH level. If the TSH level remains elevated, adjust the levothyroxine dose accordingly. If symptoms persist even when the serum TSH is within the reference range, consider discontinuing levothyroxine treatment and follow the recommended monitoring guidelines for untreated subclinical hypothyroidism and monitoring after treatment cessation. • Follow-up and monitoring should be conducted as for patients with primary hypothyroidism. • Pregnant women with TSH levels exceeding 2.5 mU/L should undergo evaluation to determine their TPO-Ab status. • In cases of subclinical hypothyroidism in pregnant patients, it is recommended to initiate low-dose levothyroxine treatment. Typically, a dose of 50 mcg/day is sufficient for effective treatment of subclinical hypothyroidism in pregnant women. • Treatment is generally not recommended when the TSH levels range from 5 to 10 mU/L. o And • Levothyroxine replacement therapy may be considered for patients with TSH levels above 10 mU/L who exhibit signs and symptoms consistent with primary thyroid disease and/or have risk factors associated with disease progression. o Or • For patients aged 2 years and above: 4. Levothyroxine treatment may be warranted for TSH levels equal to or higher than 20 mU/L. 5. Levothyroxine treatment may also be considered for TSH levels between 10 and 20 mU/L on two separate occasions spaced three months apart.

	6. For patients with TSH levels between 5 and 10 mU/L on two separate occasions spaced three months apart, and who have thyroid dysgenesis or present signs or symptoms of thyroid dysfunction, levothyroxine treatment may be appropriate. • For children aged between 28 days and 2 years, levothyroxine treatment may be initiated if the TSH level is equal to or higher than 10 mU/L. This recommendation is based on the NICE guideline. • In cases of subclinical hypothyroidism, it is advised to commence levothyroxine treatment at lower doses, typically ranging from 25 to 50 mcg. • Follow-up and monitoring should be conducted similarly to patients with primary hypothyroidism. • For adult patients with untreated or stopped treatment for subclinical hypothyroidism, follow-up should be conducted by measuring TSH and free T4 levels once a year if they exhibit features that suggest underlying thyroid disease, such as a history of thyroid surgery or elevated levels of thyroid autoantibodies. If no features suggesting underlying thyroid disease are present, follow-up can be done every 2 to 3 years. • For untreated children over 2 years old and adolescent patients with subclinical hypothyroidism (TSH < 10 mU/L), follow-up should involve measuring TSH and free T4 levels every 3 to 6 months if they have features indicating underlying thyroid disease, such as thyroid dysgenesis or elevated levels of thyroid autoantibodies. If no features suggesting underlying thyroid disease are present, follow-up can be done every 6 to 12 months. • For untreated children under 2 years old and adolescent patients with subclinical hypothyroidism (TSH < 10 mU/L), follow-up should involve measuring TSH and free T4 levels every 1 to 3 months. • For adult patients with subclinical hypothyroidism who have discontinued treatment, it is recommended to conduct follow-up by measuring TSH and free T4 levels once a year if they present features that indicate underlying thyroid disease, such as a history of thyroid surgery or elevated levels of thyroid autoantibodies. Alternatively, if there are no features suggesting underlying thyroid disease, follow-up can be done once every 2 to 3 years.

Congenital Hypothyroidism: A 2020–2021 Consensus Guidelines Update—An ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology[2]	• Congenital hypothyroidism (CH) refers to the inadequate production of thyroid hormone (TH) present at birth, resulting in a range of severity in TH deficiency. It can be attributed to abnormalities in the development or function of the thyroid gland, as well as the hypothalamus and pituitary, or impaired TH action. • Early detection and management of congenital hypothyroidism (CH) using newborn screening plays a crucial role in preventing permanent neurodevelopmental delays and promoting optimal developmental outcomes (1/+++). • The primary focus of neonatal screening for congenital hypothyroidism (CH) should be on identifying all forms of primary CH, including mild, moderate, and severe cases. The most effective test for detecting primary CH is measuring thyrotropin (TSH) (1/+++). • Additionally, when financial resources permit, it is recommended to include the measurement of total or free thyroxine (fT4) alongside TSH to screen for central CH (2/+). • A newborn who receives an abnormal result from neonatal screening should be referred to a specialized center (1/++0). • Following an abnormal screening result, confirmatory testing should be conducted, which involves measuring serum levels of free thyroxine (fT4) and thyrotropin (TSH) (1/++0). • If the serum fT4 concentration is below the age-specific reference range and TSH levels are significantly elevated, immediate initiation of levothyroxine (LT4) treatment is recommended (1/+++). • If the serum concentration of thyrotropin (TSH) is greater than 20 mU/L during confirmatory testing, which typically takes place in the second week of life, treatment should be initiated even if the free thyroxine (fT4) level is within the normal range (based on expert opinion) (2/+00). • In cases where a healthy neonate has a serum TSH concentration between 6 and 20 mU/L beyond 21 days of age, and the fT4 level falls within the age-specific reference range, we suggest two options: either commence levothyroxine (LT4) treatment immediately and retest the thyroid function after discontinuing treatment at a later stage, or defer treatment and retest after 1 to 2 weeks to reassess the need for intervention (as there is insufficient evidence to support or oppose

	treatment in this scenario, further investigation is warranted) (2/++0). • In regions or countries where thyroid function tests are not readily available, initiating LT4 treatment is advised if the filter paper TSH concentration is above 40 mU/L during neonatal screening (based on expert opinion) (2/+00). • For neonates with central congenital hypothyroidism, it is recommended to initiate LT4 treatment only after confirming intact adrenal function. If coexisting central adrenal insufficiency cannot be ruled out, LT4 treatment must be preceded by glucocorticoid therapy to prevent the potential induction of an adrenal crisis (2/+00). • For individuals who have recently been diagnosed with congenital hypothyroidism (CH), it is highly recommended to initiate levothyroxine (LT4) treatment before proceeding with thyroid gland imaging studies (1/++0). • We recommend conducting imaging of the thyroid gland using methods such as radioisotope scanning (scintigraphy) with or without the perchlorate discharge test, ultrasonography (US), or a combination of both (1/++0). Primary Congenital hypothyroidism (CH) • Levothyroxine (LT4) is the preferred medication for the treatment of congenital hypothyroidism (CH) (1/++0). • Levothyroxine (LT4) treatment should be initiated promptly, ideally within the first two weeks after birth or immediately after confirmatory thyroid function testing in neonates who have been identified with congenital hypothyroidism (CH) through a second routine screening test (1/++0). • The initial LT4 dose should be determined based on the severity of CH, considering the full spectrum from mild to severe cases (1/++0). • Infants with severe CH, characterized by very low pre-treatment levels of serum free thyroxine (fT4) (<5 pmol/L) or total T4 along with elevated thyroid-stimulating hormone (TSH) levels beyond the normal range based on age and gestational age (GA), should receive the highest starting dose of LT4 (10-15 µg/kg per day) (1/++0). • Infants with mild CH (fT4 > 10 pmol/L) and elevated TSH should receive a lower initial dose of LT4 (less than 10 µg/kg per day), and in cases where pre-treatment fT4 levels fall within the age-specific reference range, an even

	lower starting dose may be considered (between 5 and 10 µg/kg) (1/++0). • LT4 should be administered orally once daily (1/++0). The evidence regarding brand versus generic LT4 is inconclusive, but based on personal experience and expert opinion, it is recommended to use brand LT4 over generic (2/++0). • We suggest measuring serum free thyroxine (fT4) and thyroid-stimulating hormone (TSH) concentrations prior to, or at least 4 hours after, the most recent daily administration of levothyroxine (LT4) (1/++0). • We recommend evaluation of fT4 and TSH according to age-specific reference intervals (1/++0). • If the thyroid-stimulating hormone (TSH) falls within the age-specific reference range and the free thyroxine (fT4) concentrations are above the upper limit of the reference range, it is acceptable and recommended to maintain the same levothyroxine (LT4) dose (1/++0). • However, any reduction in the LT4 dose should not be solely based on a single fT4 concentration above the normal range, unless the TSH is suppressed (below the lower limit of the reference range) or there are signs of overtreatment, such as jitteriness or tachycardia (1/++0) • Unlike adults, in neonates, infants, and children, levothyroxine (LT4) can be administered together with food, if soy protein and vegetable fiber are avoided. It is important to administer LT4 at the same time every day, in relation to food intake. This approach can improve compliance and ensure consistent absorption of LT4, allowing for effective dose titration (2/+00). If there is an unexpected need to increase the LT4 dose or if there is reduced absorption or increased metabolism of thyroxine (T4) due to other diseases, the impact of food or medication should be considered (2/+00). Non-compliance is often the most common cause, especially in teenagers and adolescents. Central Congenital hypothyroidism (CH) • In severe forms of central CH (fT4 < 5 pmol/L), we also recommend starting LT4 treatment as soon as possible after birth at doses like in primary CH (10–15 lg/kg per day to normalize ft4 levels rapidly (1/++0). • In milder forms of central CH, we suggest starting treatment at a lower LT4 dose of 5 to 10 µg/kg per day to avoid the risk of overtreatment (1/++0).

	• For newborns with central CH, we recommend monitoring treatment by regularly measuring fT4 and thyrotropin (TSH) levels following the same schedule as in primary CH. The goal is to keep serum fT4 levels above the mean or median value of the age-specific reference interval. If TSH levels are low before treatment, subsequent TSH measurements may not be necessary (1/+00). • In cases where under- or overtreatment is suspected in patients with central CH, TSH, free triiodothyronine (fT3), or total triiodothyronine (T3) can be measured (1/+00). • If fT4 levels are around the lower limit of the reference interval, undertreatment should be considered, especially if TSH is above 1.0 mU/L (1/+00). • On the other hand, if serum fT4 is around or above the upper limit of the reference interval, overtreatment should be considered, particularly if there are clinical signs of thyrotoxicosis or a high fT3 concentration (1/+00). Diagnostic re-evaluation of thyroid function beyond the first 6 months of life • When no definitive diagnosis of permanent CH was made in the first weeks or months of life, then reevaluation of the HPT axis after the age of 2 to 3 years is indicated, particularly in children with a gland in situ (GIS), and in those with presumed isolated central CH (1/++0). • For a precise diagnosis, LT4 treatment should be phased out over a 4 to 6 weeks period or just stopped, and full re-evaluation should be carried out after 4 weeks, consisting of (at least) fT4 and TSH measurement. • If primary hypothyroidism is confirmed (TSH ‡10 mU/L), consider thyroid imaging and, if possible, genetic testing; if central CH is likely (fT4 below the lower limit of the reference interval in combination with a low normal of only mildly elevated TSH), consider evaluating the other anterior pituitary functions and genetic testing. • If TSH is above the upper limit of the reference interval but <10 mU/L (primary CH) or fT4 just above the lower limit of the reference interval (central CH), then continue withdrawal and retest in another 3 to 4 weeks (1/++0). • If a child with no permanent CH diagnosis and a GIS requires a LT4 dose less than 3 lg/kg per day at the age of 6 months, then re-evaluation can be done already at that time (1/++0). • We recommend avoiding iodine as an antiseptic during peri- and neonatal period, as it can cause transient CH (1/++0).

	Treatment and monitoring of pregnant women with CH • In women with CH who are planning pregnancy, we strongly recommend optimization of LT4 treatment; in addition, these women should be counseled regarding the higher need for LT4 during pregnancy (1/++0). • fT4 (or total T4) and TSH levels should be monitored every 4 to 6 weeks during pregnancy, aiming at TSH concentrations in accordance with current guidelines on treatment of hypothyroidism during pregnancy, that is, <2.5 mU/L throughout gestation in patients treated with LT4 (1/+00). • In pregnant women with central CH, the LT4 doses should be increased aiming at an fT4 concentration above the mean/median value of the trimester specific reference interval (1/+00). • After delivery, we recommend lowering LT4 dose to preconception dose; additional thyroid function testing should be performed at ~6 weeks postpartum (1/++0). • All pregnant women should ingest ~250 µg iodine per day (1/++0)
2019 European Thyroid Association Guidelines on the Management of Thyroid Dysfunction following Immune Reconstitution Therapy[3]	• We suggest that before initiating IRT, it is advisable to conduct a thyroid-stimulating hormone (TSH) test on all individuals. In cases where TSH levels are abnormal, it is also recommended to measure free-thyroxine (FT4) and, if possible, free-triiodothyronine (FT3). (1, ⌀⌀○○) • Prior or baseline thyroid dysfunction does not prevent or discourage the initiation or repetition of IRT. However, for individuals with a history of remission in Graves' disease, autoimmune hypothyroidism, or post-partum thyroiditis, it is recommended to closely monitor and investigate, if needed, under the supervision of an endocrinologist before starting IRT. (1, ⌀⌀○○) • Thyroid eye disease and cardiac conditions that pose a significant risk in the presence of thyrotoxicosis should be regarded as contraindications to initiating IRT. It is recommended to prioritize the control and treatment of these conditions before considering IRT. (1, ⌀○○○) • We do not recommend routinely measuring thyroid peroxidase antibodies (TPOAb) or thyrotropin receptor antibodies (TRAb) before initiating IRT. However, it should be noted that the risk of thyroid dysfunction is

	higher in patients who test positive for thyroid autoantibodies. (2, ⌀⌀○○) • We do not recommend routine thyroid ultrasound or scintigraphy scans before IRT (1,⌀⌀⌀○) • To assess for thyroid dysfunction following IRT, it is recommended to perform TSH testing. In addition, depending on the resources available, it may be advisable to routinely measure levels of free-thyroxine (FT4). (1, ⌀⌀⌀○) • If the initial TSH level falls within the range of 0.10–0.39 mU/L and is low, we recommend repeating the TSH test within one month. (1, ⌀⌀○○) • We recommend repeat TSH testing within 2 weeks together with FT4 if TSH is elevated, and with FT4 and FT3 if TSH is suppressed (<0.10 mU/L); a full history and examination should also be performed, focusing on thyroid signs, symptoms, and contributing factors (1,⌀⌀⌀○) • After alemtuzumab treatment, we recommend implementing regular biochemical follow-up by conducting TSH testing every three months. It is crucial not to miss these time points since thyroid dysfunction can develop rapidly. Therefore, efforts should be made to ensure that patients attend their scheduled appointments. (1, ⌀⌀○○) • It is recommended to instruct individuals undergoing IRT to promptly notify the medical team if they experience signs and symptoms of thyroid dysfunction, such as excessive sweating, unexplained weight loss or gain, nervousness, tachycardia, and increased fatigue. (1, ⌀⌀○○) • Routine TSH monitoring is not recommended following HAART (Highly Active Antiretroviral Therapy) in HIV patients. However, if clinical grounds raise suspicion of thyroid dysfunction, TSH measurement should be performed. (1, ⌀⌀○○) • It is suggested to manage the long-term follow-up of patients after bone marrow transplant (BMT) or hematopoietic stem cell transplantation (HSCT) in a specialized setting dedicated to their care. (2, ⌀○○○) • Routine measurement of thyroid function every three months is recommended and should be continued for a duration of four years following the last alemtuzumab treatment. (1, ⌀⌀○○) • Once this four-year period is completed, thyroid function testing should be conducted based on the

	presence of symptoms and signs that indicate potential thyroid dysfunction. (1, ⌀⌀○○) • During surveillance, it is not recommended to routinely measure thyroid autoantibodies in patients who have normal thyroid function (euthyroid). (1, ⌀⌀○○) • We suggest that the thyroid function of women pregnant or seeking pregnancy within 4 years of last IRT should be monitored more frequently (i.e., monthly) (2, ⌀○○○) • According to local resources and services, we suggest that these women should be immediately referred to an endocrinologist as soon as they develop TD, to be commenced on appropriate thyroid treatment and monitoring during pregnancy in a specialist setting. (2, ⌀○○○) • We recommend to promptly initiate treatment if the patient is symptomatic or at high risk (pregnancy, cardiovascular disease), or if TD persists >3 months (1, ⌀⌀○○) • In the other cases, we suggest delaying treatment by 3 months to determine if the TD spontaneously resolves, or the thyroid function fluctuates (2, ⌀○○○) • We recommend starting LT4 in patients with overt hypothyroidism. (1, ⌀⌀○○)
2021 European Thyroid Association Guidelines for the Management of Iodine-Based Contrast Media-Induced Thyroid Dysfunction[4]	• Routine baseline thyroid function testing of the general population prior to radiological examinations involving the administration of iodinated contrast media (ICM) is not recommended. (1, ⌀⌀○○) • Prior to ICM exposure, it is suggested to adopt a comprehensive case-finding approach to identify individuals with undiagnosed thyroid dysfunction. (2, ØØOO) • In high-risk patients, particularly the elderly and those at risk for cardiovascular diseases, it is recommended to measure baseline serum thyroid-stimulating hormone (TSH) levels as a screening for iodinated contrast media (ICM)-induced thyroid dysfunction. If the TSH level is abnormal, further assessment should include measuring thyroid hormones (T3 and/or T4). (2, ⌀○○○) • Patients who are receiving thyroid hormone replacement therapy are not susceptible to iodinated contrast media (ICM)-induced thyroid dysfunction and thus do not need any specific management in this regard. (1, ØOOO)

	• Routine monitoring of thyroid-stimulating hormone (TSH) levels following the administration of iodinated contrast media (ICM) is not recommended. (1, ØØØO) • The administration of iodinated contrast media (ICM) can lead to temporary alterations in serum thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3) levels in healthy individuals, typically within the normal range. When interpreting thyroid function tests, it is advisable to consider recent ICM exposure within the past 1-3 months. (2, ØØØO) • For patients suspected of iodinated contrast media (ICM)-induced hypothyroidism (Hypo), we recommend performing an initial screening test by measuring serum thyroid-stimulating hormone (TSH) levels. If the TSH level is elevated, further assessment should include measuring serum thyroxine (T4) levels. (1, ØØØØ) • In cases where the etiology of ICM-induced Hypo is unclear, it is recommended to measure serum thyroid peroxidase antibody (TPO-Ab) levels. (1, ⌀⌀○○) • For patients newly diagnosed with Hypo, it is suggested to evaluate their history of previous radiological examinations involving ICM within the past 1-2 years, as spontaneous remission may occur over time, potentially avoiding the need for lifelong levothyroxine (LT4) treatment. (2, ⌀○○○) • A personalized approach to the treatment of iodinated contrast media (ICM)-induced hypothyroidism (Hypo) is recommended, considering factors such as clinical symptoms, etiology, and the severity of Hypo, as well as the patient's age, presence of concurrent diseases, and overall clinical condition. (1, ⌀⌀○○) • In most cases of ICM-induced Hypo, close monitoring without thyroid hormone replacement is suggested. However, levothyroxine (LT4) treatment may be considered for younger patients experiencing symptoms of Hypo, those with an underlying chronic autoimmune thyroiditis, and women planning pregnancy. (2, ØØOO) • Close monitoring is advised for elderly patients who develop iodinated contrast media (ICM)-induced subclinical hypothyroidism (SHypo), with a general tendency to avoid levothyroxine treatment. (2, ØØOO • It is recommended to closely monitor thyroid function tests in infants who have been exposed to iodinated contrast media (ICM) during maternal or neonatal

	periods, with particular attention given to premature infants. (2, ØØOO)
American academy of Pediatrics Congenital Hypothyroidism: Screening and Management **(2023)**[5]	**Newborn Screening** Newborn screening (NBS) for congenital hypothyroidism (CH) should be conducted on every infant, collaborating with state or provincial public health laboratories. • For the normal newborn infant, obtain the NBS specimen after 24 hours of life (preferably between 48 to 72 hours) and before hospital discharge or 1 week of life, whichever is sooner. • If the infant is released from the hospital prior to reaching 24 hours of life, collect the NBS sample before their discharge. NBS conducted before 24 hours of life carries a higher chance of producing false-positive outcomes. If necessary, conduct the initial NBS before 48 hours of age, prior to any blood transfusion, if applicable. • There are three possible strategies for newborn screening (NBS) to detect congenital hypothyroidism (CH). These are detailed in the section regarding NBS Test Strategies in the accompanying technical report: • The first involves measuring primary TSH followed by reflex thyroxine (T4). • The second method entails primary T4 measurement with subsequent reflex TSH measurement. • The third approach combines T4 and TSH measurements. • In cases where a newborn is transferred to another hospital, the transferring institution should communicate whether the NBS sample has been collected. If it hasn't, the receiving hospital should obtain the NBS specimen following the transfer. • In situations where any NBS result indicates CH, it's recommended to conduct measurements of serum TSH and free thyroxine (FT4).

	• If the first NBS is normal, perform a second NBS at 2 to 4 weeks of age in newborns who: • are acutely ill (admitted to a NICU) • are preterm (< 32 weeks gestation) • have very low birth weight (< 1500 g) • received a transfusion before obtaining the NBS • have a monozygotic twin (or a same-sex twin, if zygosity is not known) or multiple birth • have trisomy 21 • Repeat NBS testing is recommended rather than measurement of serum TSH and FT4 because of the much lower cost of NBS. • If a second NBS performed before 36 weeks' corrected gestational age is normal, repeat NBS testing is recommended 4 weeks later (6–8 weeks of life) or at 36 weeks' corrected gestational age, whichever is earlier. • When NBS is performed after 1 week of life, use age-specific reference ranges to interpret results. NBS programs should provide age-specific reference ranges for interpretation. **Management of Abnormal NBS** • When the primary care physician (PCP) receives an abnormal NBS result for CH, a confirmatory measurement of TSH and FT4 in a serum sample should be obtained as soon as possible (within 24 hours, when possible). • Consultation with a pediatric endocrinologist is indicated, if possible, to assist in diagnosis and management. • Immediate follow-up actions are based on the TSH level of the NBS: 1) If the NBS TSH is >40 mIU/L, L-T4 treatment should be initiated after drawing the confirmatory serum sample, without waiting for the results. 2) If the NBS TSH is ≤40 mIU/L, await the results of the confirmatory serum sample (preferably with a 24-hour turnaround time), and hold off on starting L-T4 treatment. • The infant should be evaluated by a physician (PCP or pediatric endocrinologist) without delay, optimally within 24 hours or on the next office day after the NBS results are received. The physician should:

	• Obtain a complete history that includes prenatal maternal thyroid status, maternal medications, and family history. • Perform a complete physical examination. • Assess the risk of Thyroid-stimulating hormone (TSH) receptor-blocking antibodies (TRBAb) mediated hypothyroidism and consider measuring TRBAb in the infant and/or mother if there is a history of a maternal autoimmune thyroid disorder or a previous infant affected by maternal TRBAb. If TRBAb are present, no specific additional treatment is needed besides management of the hypothyroidism, and a transient course may be anticipated. • Consider obtaining imaging to establish the etiology of CH but only if the results will influence clinical management. • The subsequent steps depend on the results of the confirmatory serum sample: i. If serum TSH is high and serum FT4 is low, initiate or continue L-T4 treatment. ii. If serum TSH is greater than 20 mIU/L and serum FT4 is within the normal range, start or continue L-T4 treatment. iii. If serum TSH is elevated but less than or equal to 20 mIU/L and serum FT4 is within the normal range, you may consider initiating L-T4 treatment. Alternatively, closely monitor serum TSH and FT4 every 1 to 2 weeks without treatment. If FT4 decreases or elevated TSH persists beyond 4 weeks of age, it's recommended to start L-T4 treatment. iv. For infants with serum TSH elevation between 5 and 10 mIU/L that continues beyond 4 weeks of age, there isn't enough evidence to suggest treatment or observation. In such cases, it's advised to consult a pediatric endocrinologist to develop a patient-specific management plan if that hasn't already occurred. v. If serum TSH is within the normal or low range and serum FT4 is low, consider evaluating for possible central hypothyroidism with further testing as needed. Conduct confirmatory serum testing including TSH with FT4. Measuring thyroxine-binding globulin concentration when T4 is low but FT4 is normal might help differentiate central hypothyroidism from thyroxine-binding globulin deficiency. Infants with central CH should be assessed by a pediatric endocrinologist for additional hypothalamic-pituitary dysfunction in consultation. Consideration should be

	given to the timing of this evaluation before starting L-T4 treatment, because such treatment may lower cortisol levels. **Imaging** • Thyroid imaging is not obligatory when assessing infants with CH and can be considered if it would impact clinical decisions. The choice to proceed with imaging can be guided by consulting a pediatric endocrinologist. • Efforts to conduct imaging should never cause a delay in the treatment of CH. • Thyroid ultrasonography or scintigraphy as imaging methods might help determine the cause of CH in some cases. Nevertheless, in many situations, imaging does not modify the clinical management of the patient before the age of 3 years. **Treatment of CH** - The recommended treatment for congenital hypothyroidism (CH) involves using oral L-T4 at an initial daily dosage ranging from 10 to 15 micrograms per kilogram of body weight. - Treatment should be initiated as soon as possible after the diagnosis is confirmed (optimally by 2 weeks of age if identified on the first NBS) - Downward adjustment of the dose after laboratory evaluation at 2 weeks of age may be needed to avoid overtreatment. - Enteral administration of L-T4 tablets is the treatment of choice. L-T4 tablets can be crushed and suspended by the parent or guardian in 2 to 5 mL (~ 1 tsp) of human milk, nonsoy-containing formula, or water. A commercial oral solution of L-T4 is approved by the US Food and Drug Administration for use in children; however, limited experience with its use showed that dosing may differ slightly from dosing with tablet formulations.29,30 L-T4 suspensions prepared by compounding pharmacies may lead to unreliable dosing. - L-T4 can be given at any point during the day to infants and young children, whether in the morning or evening, with or without feeding, as long as the timing and method of administration remain constant. The presence of soy, fiber, iron, or calcium during administration can hinder L-T4 absorption. Breastfeeding can continue without disruption. In

	instances where oral administration isn't feasible, intravenous L-T4 can be given at 75% of the enteral dose. - The aim of administering L-T4 is to facilitate typical neurocognitive development and growth. Attaining the best possible results hinges on promptly starting appropriate L-T4 treatment, ideally within the first two weeks of life when identified through the initial newborn screening (NBS), especially in instances of severe CH. - Once the initial normalization is achieved, serum TSH levels should be kept within the reference range appropriate for the individual's age. Additionally, serum FT4 levels should be maintained in the upper half of the age-specific reference range, unless maintaining a serum FT4 level within this range would lead to a TSH level falling below the reference range. - Ideally, the same L-T4 formulation should be maintained consistently until 3 years of age to achieve consistent euthyroidism and minimize the need for additional laboratory monitoring. If feasible, the use of a brand name L-T4 formulation to provide a consistent formulation may be superior for children with severe CH.43 If generic L-T4 is prescribed, it is preferable to use L-T4 from a consistent manufacturer. - Using liothyronine treatment is typically not recommended. The application of liothyronine in individuals with ongoing severe resistance to thyroid hormone (elevated TSH despite elevated FT4), who can't achieve sufficient control through L-T4 alone, hasn't been shown to enhance outcomes. This option should only be contemplated under the guidance of a pediatric endocrinologist. **Monitoring** - Throughout the initial three years of life, consistent clinical assessment should be carried out as outlined below. This assessment involves evaluating developmental advancements and growth, as detailed in the Monitoring section of the accompanying technical report. - Due to the heightened likelihood of hearing impairments in those with CH, a formal hearing evaluation should be contemplated whenever clinical indications of hearing issues or atypical language development arise. - Serum TSH and FT4 should be measured:

	5. One to 2 weeks after the initiation of L-T4 treatment and every 2 weeks until serum TSH level is normal 6. Every 1 to 2 months during the first 6 months of life (monthly in infants with severe CH [initial serum TSH >100 mIU/L or FT4 < 0.4 ng/dL]) 7. Every 2 to 3 months during the second 6 months of life; and 8. Every 3 to 4 months between 1 and 3 years of age. **Long-Term Follow-Up** After 3 years of age, measurement of TSH is recommended: 4. Every 6 to 12 months until growth is complete; 5. Four to six weeks after any change in LT-4 dose or formulation; and 6. At more frequent intervals in children with severe CH, problems with adherence to the L-T4 treatment plan, or TSH levels outside the age-specific reference range. D. After 3 years of age, monitoring of TSH is sufficient. FT4 may be measured if medication adherence or suboptimal control is a concern. E. After the first 3 years of life, clinical evaluation and assessment of growth and development should be performed every 6 to 12 months **Assessment of the Permanence of Hypothyroidism** - Permanent congenital hypothyroidism (CH) is verified in situations involving thyroid dysgenesis or if the serum TSH rises above 10 mIU/L after the initial year of life. - Lifelong L-T4 therapy. Is required for patients with permanent CH. - If a definitive diagnosis of permanent congenital hypothyroidism (CH) hasn't been established, it's advisable to seriously contemplate discontinuing L-T4 therapy when the child reaches 3 years of age, especially if they are effectively managed with a low L-T4 dosage (<2 mcg/kg/day). A trial off L-T4 may be conducted as follows: 6. Discontinue L-T4 for 4 weeks, then measure serum TSH and FT4 levels. 7. If TSH and FT4 levels remain in the age-specific reference range, transient CH is confirmed. 8. If the TSH is >10 mIU/L and/ or FT4 is low, permanent CH is confirmed and LT-4 therapy should be reinstituted.

	9. If the TSH is mildly elevated (greater than the age-specific reference range, but #10 mIU/L) and FT4 is normal, repeat serum TSH and FT4 levels in another 4 to 8 weeks to determine if there is (1) normal thyroid function (indicating transient CH), (2) permanent CH (TSH >10 mIU/L or low FT4), or (3) persistent hyperthyrotropinemia (TSH persistently elevated but ≤ 10 mIU/L, with normal FT4). There is insufficient evidence to determine if the treatment of persistent hyperthyrotropinemia is of clinical benefit, but many practitioners elect to treat it out of caution. 10. It is critical that patients not be lost to follow-up while trialing off L-T4 therapy.

Appendix C. MeSH Terms PubMed

PubMed Search for Hypothyroidism

Query	Search Details	Filters	Results
((((((((((((((((Hypothyroidism[MeSH Terms]) OR (Hypothyroidisms[Title/Abstract])) OR (Primary Hypothyroidism[Title/Abstract])) OR (Hypothyroidism, Primary[Title/Abstract])) OR (Primary Hypothyroidisms[Title/Abstract])) OR (Thyroid-Stimulating Hormone Deficiency[Title/Abstract])) OR (Deficiency, Thyroid-Stimulating Hormone[Title/Abstract])) OR (Hormone Deficiency, Thyroid-Stimulating[Title/Abstract])) OR (Thyroid Stimulating Hormone Deficiency[Title/Abstract])) OR (Thyroid-Stimulating Hormone Deficiencies[Title/Abstract])) OR (TSH Deficiency[Title/Abstract])) OR (Deficiency, TSH[Title/Abstract])) OR (TSH Deficiencies[Title/Abstract])) OR (Secondary Hypothyroidism[Title/Abstract])) OR (Hypothyroidism, Secondary[Title/Abstract])) OR (Secondary	("Hypothyroidism"[MeSH Terms] OR "Hypothyroidisms"[Title/Abstract] OR "primary hypothyroidism"[Title/Abstract] OR "hypothyroidism primary"[Title/Abstract] OR "primary hypothyroidisms"[Title/Abstract] OR "thyroid stimulating hormone deficiency"[Title/Abstract] OR "deficiency thyroid stimulating hormone"[Title/Abstract] OR "hormone deficiency thyroid stimulating"[Title/Abstract] OR "thyroid stimulating hormone deficiency"[Title/Abstract] OR "thyroid stimulating hormone deficiencies"[Title/Abstract] OR "tsh deficiency"[Title/Abstract] OR "deficiency tsh"[Title/Abstract] OR "tsh deficiencies"[Title/Abstract] OR "secondary hypothyroidism"[Title/Abstract] OR "hypothyroidism secondary"[Title/Abstract] OR (("neoplasm	Guideline, in the last 5 years	6

Hypothyroidisms[Title/Abstract])) OR (Central Hypothyroidism[Title/Abstract])) OR (Central Hypothyroidisms[Title/Abstract])) OR (Hypothyroidism, Central[Title/Abstract])	metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "secondaries"[All Fields] OR "Secondary"[MeSH Subheading] OR "Secondary"[All Fields]) AND "Hypothyroidisms"[Title/Abstract]) OR "central hypothyroidism"[Title/Abstract] OR (("Central"[All Fields] OR "centrally"[All Fields] OR "centrals"[All Fields]) AND "Hypothyroidisms"[Title/Abstract]) OR "hypothyroidism central"[Title/Abstract])		

Appendix D. Treatment Algorithm