

2022 European Thyroid Association Guideline for the management of pediatric Graves' disease.

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04 11 2021 01 2 2022 11 1 408677 e210073 27 10 2021 04 11 2021 04 11 2021 31 05 2022 12 06 2022 © European Thyroid Association 2022 The authors <https://creativecommons.org/licenses/by-nc-nd/4.0/> This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. . Hyperthyroidism caused by Graves' disease (GD) is a relatively rare disease in children. Treatment options are the same as in adults – antithyroid drugs (ATD), radioactive iodine (RAI) or thyroid surgery, but the risks and benefits of each modality are different. The European Thyroid Association guideline provides new recommendations for the management of pediatric GD with and without orbitopathy. Clinicians should be alert that GD may present with behavioral changes or declining academic performance in children. Measurement of serum TSH receptor antibodies is recommended for all pediatric patients with hyperthyroidism. Management recommendations include the first-line use of a prolonged course of methimazole/carbimazole ATD treatment (3 years or more), a preference for dose titration instead of block and replace ATD, and to avoid propylthiouracil use. Where definitive treatment is required either total thyroidectomy or RAI is recommended, aiming for complete thyroid ablation with a personalized RAI activity. We recommend avoiding RAI in children under 10 years of age but favor surgery in patients with large goiter. Pediatric endocrinologists should be involved in all cases.

Hyperthyroidism caused by Graves' disease (GD) is a relatively rare disease in children. Although treatment options are the same as in adults – antithyroid drugs (ATD), radioactive iodine (RAI) and thyroid surgery – the benefits and risks of each modality are different in the young. The European Thyroid Association (ETA) guideline addresses the etiology, diagnosis and prognosis of pediatric GD patients with and without orbitopathy and includes evidence-based treatment recommendations. Fetal and neonatal thyroid dysfunction related to maternal GD during pregnancy is not discussed in this guideline.

A taskforce of European clinician scientists led by a chairman (ASPvT) was established. For three important clinical/treatment topics in pediatric GD, a systematic literature search and evaluation were performed: remission rate and adverse effects associated with ATD treatment; efficacy and safety of RAI; efficacy and safety of thyroidectomy. For additional questions, targeted literature searches were performed. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was used for rating the strength of the recommendations and the quality of the underlying evidence (1). We used the following coding system: '1', strong recommendation and '2', weak recommendation or suggestion. The quality of the evidence is rated as level 'ØØØØ' – high, level 'ØØØØ' – moderate , level 'ØØØØ' – low, or level 'ØØØØ' – very low. The drafted guideline version was discussed within the task force until consensus was reached. The recommendations are listed in Table 1 . Table 1 European Thyroid Association 2022 recommendations for the management of pediatric Graves' disease.

Hyperthyroidism is a pathological state characterized by increased synthesis and secretion of thyroid hormones (thyroxine (T4) and triiodothyronine (T3)) by the thyroid gland (2). Thyrotoxicosis refers to the clinical picture of thyroid hormone excess. In childhood, most cases of hyperthyroidism are caused by underlying thyroid disease with high serum free T4 (FT4) or free T3 (FT3) concentrations and a fully suppressed thyrotropin (TSH; <0.1 mIU/L) (3 , 4). This is known as overt primary hyperthyroidism. Subclinical hyperthyroidism – a milder form – is defined as a low or suppressed TSH (<0.4 mIU/L), but serum free T4 (FT4) and free T3 (FT3) within the reference interval.

In children, hyperthyroidism is mostly caused by GD and is usually biochemically overt and clinically severe (4). The characteristics of GD and other possible causes of hyperthyroidism and thyrotoxicosis in children are shown in Table 2 . Signs and symptoms of hyperthyroidism in children are similar to those in adults. Childhood hyperthyroidism may also cause accelerated growth and bone maturation and deterioration in academic performance (4). In healthy children, thyroid size at physical and ultrasound examination increases with age (5), but in GD, the thyroid is frequently symmetrically enlarged. Increased thyroidal blood flow may result in a thrill or bruit. Manifestations of thyroid eye disease include proptosis and lid retraction and are as common in children as in adults, but inflammatory features are less severe (6 , 7). In many pediatric GD patients, there is a diagnostic delay due to suspected behavioral, gastrointestinal, respiratory or cardiac disease. Table 2 Causes of pediatric hyperthyroidism/thyroid hormone excess a .

a An important diagnostic pitfall is the false biochemical picture of hyperthyroidism due to interference with laboratory testing, for example, by biotin.

b Deliberate or inadvertent (e.g. as a component of multivitamin supplement).

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; T3, tri-iodothyronine; T4, thyroxine; Tg, thyroglobulin; TSH, thyrotropin; TSHRab, TSH receptor antibodies; TSI, thyroid-stimulating immunoglobulins; TPO, thyroid peroxidase; US, ultrasonography.

In all pediatric patients with suspected hyperthyroidism, serum FT4, FT3 and TSH should be measured. Since GD is the most frequent cause of hyperthyroidism, anti-TSH receptor and anti-thyropoxidase antibodies (TSHRab – also known as thyroid-binding inhibitory

immunoglobulin or TBII – and anti-TPO, respectively) should also be measured (4). An elevated FT3 level is a more sensitive marker of overt hyperthyroidism than FT4. This biochemical evaluation will confirm or refute the diagnosis of pediatric GD in most cases (Table 2). If the clinical picture is suggestive of GD but thyroid antibodies are absent, they should be repeated a few weeks later. If there are still no signs of thyroid autoimmunity, thyroid ultrasonography, scintigraphy – preferably with Tc-99m-pertechnetate – and additional laboratory investigations can be considered (Table 2). To avoid radiation exposure, thyroid ultrasonography with Doppler blood flow assessment is preferred over scintigraphy (8), but scintigraphy is better for diagnosing a ‘hot’ autonomous nodule and excluding low iodine uptake thyrotoxicosis.

GD is an autoimmune disorder characterized by the presence of TSHRAb resulting in an overactive thyroid gland (Graves’ hyperthyroidism), ocular abnormalities (Graves’ orbitopathy, GO) and – very rarely – localized dermopathy (pretibial myxoedema, PTM) (9). TSHRAb act as agonist, induce excessive thyroid hormone secretion and uncouple the thyroid from pituitary control (10). They also stimulate thyroid gland growth via similar, but not identical, signal transduction. In the orbit, TSHRAb stimulation of fibroblasts expressing TSHR induces hyaluronan production, potentiated by cross-talk between TSHR and insulin-like growth factor 1 receptors. This is accompanied by retro-orbital inflammation, extraocular muscle fiber disruption and tissue edema (11). Finally, TSHR stimulation induces fibroblasts to differentiate into adipocytes, resulting in tissue expansion in the orbit (12).

The etiopathogenesis of GD is not fully understood. Genetically determined immunological susceptibility appears to interact with environmental insults (e.g. cigarette use, infection, stress and gut microbiota). Genetic susceptibility is linked to the HLA locus and other immune-related genes (e.g. CTLA4, IL-2RA and PTPN22) and thyroid-specific genes (e.g. TG and TSHR) (13 , 14 , 15). HCP5 polymorphisms have been associated with a younger age at GD onset (16 , 17). GD is associated with the occurrence of other autoimmune disorders such as type I diabetes mellitus, celiac disease and vitiligo and is more common in Down syndrome (4 , 18). In approximately 15% of cases, there is a first-degree relative with autoimmune thyroid disease. GD can also occur following bone marrow transplantation and HIV therapies (19).

Childhood GD accounts for 5% of all GD cases throughout life (20). The overall incidence in children and adolescents is around 4.58/100,000 per year, but before age 15 years, the incidence is lower: 1 to 2.91/100,000 per year. GD is 3.4 times more common in girls than boys (21). Before age 5 years, the prevalence is about ten times lower, with a girls-to-boys ratio of 1.4. This ratio increases markedly with age, particularly in the second decade of life (21 , 22). GD incidence varies between countries and may be rising (23 , 24).

Because of deleterious effects of excess thyroid hormone on multiple organ systems, children with GD require prompt treatment. Occasional, evolving ‘mild’ cases, including subclinical hyperthyroidism with minimal clinical and biochemical disturbance, may benefit from a period of surveillance to clarify the need for treatment.

In general, initial treatment is medical. When this fails or is not possible, a definitive treatment should be considered. The proposed approach to treatment and follow-up is a general one and – depending on specific patient characteristics – can be individualized.

The thionamide carbimazole (CBZ) or its active metabolite methimazole (MMI; also known as thiamazole) can be used to treat hyperthyroidism. Propylthiouracil (PTU) should not be used because of the risk of hepatic failure (25). Thionamides act as a preferential substrate for thyroid peroxidase (TPO), thereby preventing tyrosine iodination in the thyroglobulin molecule and blocking thyroid hormone synthesis. Although a direct immunomodulatory action has been proposed (26), rendering the patient euthyroid has a beneficial effect on autoimmunity in itself (27).

ATD can be titrated against thyroid function tests (dose titration, DT) or administered in a larger dose to prevent endogenous thyroid hormone production, with levothyroxine (LT4) added later in a replacement dose (block and replace, BR). The ATD starting dose will depend on weight, signs, symptoms and biochemical severity.

MMZ of 0.6 mg is approximately equivalent to 1.0 mg CBZ. MMZ of 0.5 mg/kg or CBZ of 0.75 mg/kg will block thyroid hormone production in the majority of patients. A lower starting dose of 0.15 mg/kg of MMZ or 0.25 mg/kg CBZ can be used in mild to moderate disease (e.g. FT4 $\leq$ 35 pmol/L or FT3 $\leq$ 12 pmol/L). MMZ/CBZ can be administered once daily (28 , 29 , 30).

A starting dose of 0.15–0.3 mg/kg MMZ or 0.25–0.5 mg/kg CBZ will normalize thyroid hormone concentrations in most patients with the dose then reduced to prevent hypothyroidism. Larger ATD doses (0.5 mg/kg MMI or 0.75 mg/kg CBZ) can be administered in more severe cases where a more rapid reduction in thyroid hormone concentrations is desirable. The ATD dose required to maintain euthyroidism will depend on disease severity. TSHRAb concentrations fall during ATD therapy and so the ATD dose can sometimes be reduced to 2.5–5 mg MMZ or CBZ daily in the longer term.

A dose of 0.3–0.5 mg/kg MMZ or 0.5–0.75 mg/kg CBZ will usually result in hypothyroidism. LT4 in an age and weight-appropriate replacement dose should be started when thyroid hormone levels normalize/before hypothyroidism supervenes. Higher ATD doses (e.g. 1.0 mg/kg MMZ or 1.3 mg/kg CBZ) can be used initially in severe disease or if thyroid hormone concentrations do not fall as expected.

A recent RCT showed no difference in biochemical control between DT and BR, but more adverse events in BR (31). Therefore, in most cases, DT is preferred. Earlier studies can be interpreted as demonstrating greater biochemical stability with BR (32 , 33 , 34), and there may be occasions when the pediatric endocrinologist discusses the theoretical advantages of BR with families.

A beta-blocker (e.g. propranolol or atenolol) should be administered in an age- or weight-appropriate dose when there are signs of moderate to severe thyroid hormone excess (35) but are contraindicated in patients with asthma. The beta-blocker can be stopped once thyroid hormone levels normalize.

Occasionally, patients with GD present with a thyroid crisis or 'storm'. The associated clinical picture includes tachycardia, heart failure, hyperthermia, extreme anxiety, altered mental state and gastrointestinal upset. This may arise in untreated GD or be precipitated by additional factors such as infection, surgery or RAI therapy. In these circumstances, euthyroidism can be reached more rapidly by administering iodine (e.g. potassium iodide solution) and a glucocorticoid, in addition to ATD and a beta-blocker. ATD and iodine (ATD an hour before iodine to stop the release of preformed thyroid hormone) are used to block thyroid hormone synthesis and secretion, while glucocorticoids inhibit the peripheral conversion of the (inactive) prohormone T4 to metabolically active T3. Beta-blockers attenuate the peripheral adrenergic actions of the thyroid hormone. Patients in thyroid storm should be managed in a high or intensive care setting. The possibility that iodine administration may complicate RAI treatment or result in hyperthyroidism at a later stage needs to be considered. In general, GD patients should avoid excess nutritional iodine intake because this may aggravate hyperthyroidism.

Tables 3 and 4 describe frameworks for managing patients with DT and BR, respectively. Patients can be seen and thyroid status can be assessed every 4 weeks for the first 3 months, moving to 2- to 3-monthly assessments thereafter. Table 3 Framework for managing patients with dose titration.

ATD, antithyroid drug; CBZ, carbimazole; FT3, free triiodothyronine; FT4, free thyroxine; kg, kilogram; MMI, methimazole; TSH, thyrotropin; TSHRAb, TSH receptor antibodies.

Framework for managing patients with block and replace.

ATD, antithyroid drug; CBZ, carbimazole; FT3, free triiodothyronine; FT4, free thyroxine; LT4, levothyroxine; MMI, methimazole; TSH, thyrotropin; TSHrAb, TSH receptor antibodies.

Hyperthyroidism can, like ATD, be associated with a low white cell count and hepatic dysfunction (36 , 37). A full blood count (FBC) and liver function should therefore be assessed pre-treatment so that subsequent investigations can be placed into context. The timing of FBC/liver function assessments while on ATD is discussed in more detail below.

Most patients will be biochemically euthyroid within 4–6 weeks, although the timeline will depend on disease severity, ATD dose and compliance. Patients with higher baseline thyroid hormone concentrations may take a longer time to normalize. Moreover, ATDs build up in the thyroid over a few weeks, and improvement in symptoms may not be immediate.

Although most patients have a BMI SD score within normal limits at diagnosis, excessive weight gain can occur after euthyroidism is restored (38).

Around 15% of pediatric GD patients on ATD (mainly MMI/CBZ) develop at least one side effect/adverse event (AE) (Supplementary Table 1, see section on supplementary materials given at the end of this article). The most frequent minor side effect is a cutaneous reaction (pruritic rash and urticaria; ≈10%). Hepatitis/liver dysfunction with CBZ/MMI is cholestatic and resolves when ATD is stopped (39), in contrast to the hepatocellular damage seen with PTU. Major side effects like agranulocytosis are reported very rarely in pediatric GD patients (40). The majority of AEs occur in the first 3 months with a higher rate in younger children (41 , 42). Severe AEs may be dose-dependent (27).

Patients and families should be counseled about ATD side effects. In case of agranulocytosis/severe neutropenia, the patient should stop ATD and undergo determination of neutrophil count in the event of signs or symptoms of infection like fever or a sore throat. ATD-associated neutropenia typically develops in the first month of treatment (median 30 days), although there are rare cases of patients developing neutropenia after many years on treatment (43). Management is complicated by the fact that a low neutrophil count can reflect the disease process or recent infection. If the neutrophil count is below $0.5 \times 10^9/L$, then the ATD should be stopped and alternative treatment should be initiated. A neutrophil count between 0.5 and 1.5 can be monitored closely with once or twice weekly measurements. Some ATD side effects such as rash can be managed symptomatically knowing that they usually settle spontaneously, although, in the presence of mucosal blistering, which may herald Stevens–Johnson syndrome, ATD should be stopped immediately (42 , 44). An increased transaminase level (>three times the upper limit of normal) during treatment warrants ATD cessation and so liver function tests should be performed in the event of pertinent signs of liver dysfunction (4). MMI/CBZ should not be recommenced in an individual who has experienced a serious complication linked to earlier MMI/CBZ administration.

Occasionally, patients remain thyrotoxic on doses of MMI/CBZ in excess of 0.6 mg/kg/day or 1 mg/kg/day, respectively. Compliance and exacerbation by the use of iodine-containing supplements should be discussed. The risk of adverse events may increase with higher doses, and while the ATD dose can be increased to 1.0 mg/kg/day (MMI) or 1.3 mg/kg/day (CBZ), it is appropriate to discuss the role of surgery or RAI with families as well (45).

Total thyroidectomy or RAI is the treatment options for patients who develop ATD side effects such as severe neutropenia or significant liver dysfunction. These treatments may also be selected if the patient or parents are unable to report ATD side effects (e.g. learning disability), if they have relapsed and do not want further ATD, or where there is long-standing poor compliance.

When considering whether ATD should be stopped, TSHRAb can be used to predict the likelihood of relapse. If the TSHRAb titer is elevated, then remission is unlikely (46).

The overall remission rate after 2 years of ATD treatment in pediatric GD patients is 20–30% (40 , 47). The remission rate increases with longer treatment duration. Remission rates of 24.1, 31.0 and 43.7% are reported after treatment durations of 1.5–2.5, 2.5–5 and 5–6 years, respectively (40 , 48). One study with a treatment duration of 9 years reported a remission rate of 75% (Fig. 1) (49). Figure 1 Remission rates in relation to duration of medical treatment (methimazole or carbimazole) in patients with pediatric Graves' disease. Remission rates reported in the systematic review by van Lieshout et al. (40) (Table 2) evaluating studies on the efficacy of treatment with methimazole or carbimazole in relation to the treatment duration in pediatric Graves' disease. Size of the bubble reflects the size of the patient population. Prospective studies comparing standard and long-term treatment durations are displayed twice in this figure (Azizi et al . (49) displayed in red, and Léger et al . and Kaguelidou et al . (47 , 48) displayed in green).

Treatment duration should be at least 3 years and potentially 5 years or longer if the likelihood of remission is low based on patient characteristics at presentation (Table 5). ATD can be continued for many years although the likelihood of long-term remission if ATD were stopped should be discussed regularly with families. Those patients who are likely to remit when ATD are stopped will usually be on a low dose of ATD and have no detectable TSHRAbs. TSHRAb decline by a median of 90% after 3 years of ATD treatment and ATD should not be stopped if TSHRAb are raised (46 , 50). Patients who relapse when ATD is stopped usually do so within 12 months (47), and so treatment cessation should not usually be in the period leading up to key educational milestones such as examinations. Table 5 Factors associated with improved likelihood of remission following antithyroid drug treatment.

ATD, antithyroid drug; TSHRAb, TSH receptor antibodies.

Patients and families should be familiar with the manifestations of thyrotoxicosis, and patients should have thyroid function checked if relapse is suspected, or every 3–4 months after stopping ATD in the first year, every 6 months in the second year and annually thereafter; not only because of the risk of relapse but also of autoimmune hypothyroidism (see prognosis) (51). Patients can be referred back to their family doctor after 12–24 months, with advice to monitor thyroid function for at least 10 years or in case of symptoms or signs of hyperthyroidism. The possibility of TSHRAb crossing the placenta and affecting the health of the fetus years later should be discussed with females pre-discharge and reinforced by pertinent text in associated correspondence. Evaluation of thyroid function pre-conception and TSHRAb levels when pregnant (especially after definitive treatment for GD) is needed.

Some patients who relapse may still remit in the long term depending on associated features (Table 5). This should be taken into consideration when considering the role of further ATD.

There are case reports and series describing the clinical course of adult patients receiving biologics like rituximab or TSHR-blocking antibodies (K1-70) as a treatment for GD (52 , 53 , 54 , 55 , 56 , 57 , 58). There is insufficient evidence to suggest that these agents are of benefit in pediatric GD.

Indications for definitive treatment include relapse after ATD treatment, serious or persistent side effects of ATD, poor compliance or obstructive symptoms from a large goiter (4 , 59 , 60).

Like iodine, RAI is taken up and metabolized by the thyrocyte and stored within the thyroid follicle as thyroid hormone. Isotope decay with the emission of beta-radiation damages thyrocyte DNA resulting in apoptosis and tissue necrosis. Sufficient RAI activity will destroy the thyroid gland resulting in hypothyroidism.

When RAI is chosen as definitive treatment, we advise aiming for thyroid ablation in order to minimize the risk of relapse and (future) malignant transformation of persistent, viable but radiation-damaged cells.

When administering RAI, there are various methods for calculating appropriate activity, including a fixed approach with activities ranging from 200 to 800 MBq (61), limited personalization in the form of (preferably) 15 MBq I-131 per gram thyroid tissue (thyroid volume/weight estimated by ultrasound) (62) or dosimetry aiming at delivering at least 300 Gy to the thyroid gland for functional ablation (61). No method is demonstrably superior to others, although higher activities/doses are usually associated with higher rates of complete functional ablation. No adult or pediatric studies demonstrate a 100% success rate. For the greatest chance of success, while at the same time minimizing excessive radiation exposure, we recommend performing thyroid dosimetry if available.

RAI can theoretically be used in any patient with GD, but contraindications are pregnancy (and becoming pregnant within 6 months after RAI), breast-feeding, young age (<5 years; because of a greater long-term theoretical risk of malignancy) and active GO which can be exacerbated by RAI. Relative contraindications are age 5–10 years, inactive GO and large goiter that may need repeated treatment.

Side effects following RAI treatment in pediatric GD patients are extremely rare, although sometimes a mild tenderness over the thyroid may be observed in the first week after treatment. Observational studies in pediatric patients treated with RAI aiming at hypothyroidism reported no malignancies or fertility problems with a maximum follow-up of nearly four decades (59 , 63 , 64 , 65).

Measures to be considered when preparing a pediatric patient for RAI are shown in Supplementary Table 2. ATD should be stopped 3–7 days prior to RAI administration. Patients with active GO should receive a course of steroids in accordance with EUGOGO guidelines (66). RAI should be administered according to local radiation protection law. After RAI, ATD treatment should be resumed 1–2 days after I-131 administration and continued for at least 3 months if a BR strategy is used, or titrated against thyroid hormone concentrations. TSH levels may not normalize for several months after RAI treatment. Patients and parents should be warned about a small risk of thyroid crisis post RAI treatment (67), although this is extremely rare in children (65). The first clinical and biochemical evaluation by the pediatric endocrinologist should be scheduled 4–6 weeks after RAI administration but can be brought forward depending on the pre-RAI treatment status. As the objective of RAI is complete thyroid ablation, lifelong LT4 replacement is usually necessary. If hyperthyroidism still persists at 12 months after RAI, a second course can be considered.

Total thyroidectomy aims to remove all overactive thyroid tissue. It is the preferred definitive treatment option for GD patients younger than 10 years, for patients with a (relative) contraindication for RAI treatment and for those with a large or nodular goiter. The advantage of total thyroidectomy is that it immediately cures hyperthyroidism by removing the source of excess thyroid hormone. Subsequent hypothyroidism necessitates lifelong LT4 treatment. Total thyroidectomy is preferred over subtotal thyroidectomy to reduce the risk of recurrent hyperthyroidism, with no reported difference in complications (68 , 69).

Prior to surgery, patients need to be biochemically euthyroid to reduce the risk of anesthesia and thyroid storm. ATD treatment should be continued until the day of surgery. When euthyroidism cannot be achieved by ATD treatment alone, oral iodine (5–10 drops of Lugol's solution or 1–4 drops of saturated potassium iodide solution three times daily) can be administered for 1–2 weeks prior to surgery to normalize FT3. If surgery is not performed in a timely manner, then the patient may become thyrotoxic again. Pre-operative treatment with a beta-blocker and glucocorticoid may be required (2). Patients should be vitamin D replete prior to surgery to reduce the risk of post-operative transient hypocalcemia and if in doubt can be treated with cholecalciferol for 3 days prior to surgery (60). After total thyroidectomy, LT4 treatment should be commenced in a weight-appropriate dose.

Mortality post-thyroidectomy in pediatric GD patients is very low (<0.1%). However, there are post-operative morbidities, including transient hypocalcemia (22.2%) and recurrent laryngeal nerve (RLN) injury (5.4%) (70). In addition, permanent hypoparathyroidism with hypocalcemia was reported in 2.5% and permanent RLN in 0.4% of pediatric GD patients (70). Post-operative infection, hemorrhage and keloid development are rare. Damage to the superior laryngeal nerve's external branch may occur after thyroidectomy and can have subtle effects on voice projection (71). The risk of post-operative morbidities is lower when thyroidectomy is performed by a high-volume thyroid surgeon.

The choice for RAI or total thyroidectomy is a contentious topic and will reflect local opinion and expertise. Each pediatric case warrants interdisciplinary consultation including a pediatric endocrinologist, thyroid surgeon and nuclear medicine physician specialized in thyroid disease; the choice of definitive treatment will involve shared decision making with the patient and the parents/legal guardians, focusing on the advantages and disadvantages of each option.

An absolute or relative contraindication for one modality vs another such as pregnancy or a markedly elevated risk of perioperative morbidity may direct treatment choice. Table 6 lists contraindications for and advantages and disadvantages of RAI and total thyroidectomy. Table 6 Specific indications and contraindications for, and pros and cons of, definitive treatment in pediatric Graves' disease: radioactive iodine vs surgery/total thyroidectomy.

ATD, antithyroid drug; GO, Graves' orbitopathy; RAI, radioactive iodine; TSHRAb, anti-TSH receptor antibodies.

Pediatric GO is caused by autoreactivity to TSHR. Hyperthyroid children with GD and GO have higher TSHRAb levels than those with only hyperthyroid GD, and during ATD treatment, TSHRAb decreases less in children with GO (46 , 72). The pathogenesis of GO is therefore the same in children as in adults (10).

The frequency of GO in pediatric GD patients is 27–63% and is similar to adults (47 , 72 , 73 , 74 , 75 , 76 , 77). In 19–69%, family members also have thyroid dysfunction (78 , 79 , 80). Female-to-male ratio is between 3.3 and 7.1 to 1 (75 , 76 , 78 , 79 , 81). The time between diagnosing thyroid dysfunction and the onset of eye signs is usually less than 6 months. Like in adults, independent risk factors for GO are smoking (OR = 7.098), TSHRAb (OR = 6.358), stress (OR = 6.030) and high FT4 at diagnosis (OR = 5.963) (82).

Eyelid retraction (median 72%; range 23–91%) and proptosis (median 53%; range 4–92%), best detected by comparison with photographs prior to the onset of GO, are the most frequent signs of GO in children with GD; soft tissue inflammation is less common (median 22%; range 1–59%). In most retrospective and cross-sectional studies, impaired motility and dysthyroid optic neuropathy are rare or not reported, respectively. Accordingly, most patients have a mild course (7).

In most retrospective case series and cross-sectional studies, pediatric GD patients with GO are managed conservatively (70–100%) because of mild underlying disease (79 , 80). In patients with lagophthalmos artificial tears can be offered, but with good tear production and absence of meibomian gland dysfunction, eye drops and ointments are rarely needed. Rare cases of moderate-to-severe active GO cases can be treated with anti-inflammatory drugs (e.g. i.v. corticosteroids) (66). Selenium (Se) supplementation can prevent further deterioration in adults and can be offered to children when residing in an area of limited Se intake (83). A daily supplementation dosage of 1–2 µg/kg can be administered for 6 months (84).

Improvement of GO with normalization of thyroid function is frequently reported (7). Few patients need surgery (lid lengthening and rarely orbital decompression). Decompression surgery is best deferred until the facial skull has fully grown. Success rates are the same as in adults (85 , 86).

Pediatric patients with GO are more likely to have a severe course of their GD and are less likely to go into remission following ATDs (77). Thyroid surgery is preferable to RAI treatment in active GO, and if there is a poor/absent response to GO treatment, then thyroidectomy may also reduce the risk of GO exacerbation (66 , 87).

In 2–10% of adults undergoing thyroidectomy for GD, co-existing differentiated thyroid cancer (DTC) is found in surgical specimens (88). In 80% of cases, these are incidental microcarcinomas (<10 mm in diameter), reflecting modern, detailed histological analysis. In some but not all studies, the rate of thyroid cancer detected is the same in adult GD patients as in those undergoing thyroidectomy for other benign thyroid diseases (89). However, several studies have found a slightly higher DTC rate in GD patients. Cappelli et al . found a cancer rate of 6.5% in GD patients undergoing thyroidectomy compared to 4.4% of those with solitary toxic nodules (90), and some studies found that tumors in adult GD patients may behave more aggressively (91 , 92 , 93). A meta-analysis of 987 GD patients with DTC confirmed the higher prevalence of adverse prognostic features, but there was no difference in persistent disease or mortality (94). Several mechanisms have been postulated for these associations including the stimulation of thyrocyte proliferation by TSHRABs and increased vascularity.

Despite the associations found in adults with Graves' disease, there is little information on this subject in pediatric GD patients. A retrospective analysis of young GD patients undergoing thyroidectomy at a single North American center showed that 7 of 32 (22%) had differentiated thyroid cancer (95). In four patients, this was suspected from ultrasound and cytological workup pre-operatively, but in three, this was an incidental finding. The young patients with GD did not appear to have a worse prognosis than age-matched patients without GD (96).

Additional work is required, but in the interim, we recommend that all palpable thyroid nodules in children and adolescents with GD are subject to ultrasound evaluation. Patients with suspicious sonographic findings should either proceed to FNA cytological assessment or direct to total thyroidectomy. There is little role for 'diagnostic surgery' in this situation with total thyroidectomy the best treatment option.

It is important to discuss the various possible outcomes when managing GD. The first treatment goal is to restore euthyroidism. The most favorable long-term outcome is permanent functional and immunological remission without the need for medical treatment. Unfortunately, many children have a less favorable outcome: persistent thyroid autoimmunity and thyroid stimulation by TSHRAB necessitate lengthy medical, or definitive thyroid destructive therapy. Hence euthyroidism is achieved by long-term ATD or, after definitive treatment, by thyroid hormone replacement. Some children in remission may require thyroid hormone replacement at a later stage because of co-existing Hashimoto disease that evolves into hypothyroidism. Long-term follow-up studies in adults showed approximately one-quarter of patients in remission develops subclinical or overt Hashimoto hypothyroidism (97). Data on this in children are lacking. For young people/families opting for definitive treatment and thyroid hormone replacement, the aforementioned advantages and disadvantages of RAI and surgery need to be considered; the treating physician has an important role in counseling patients and parents.

Another important long-term outcome is quality of life (QoL). In a recent study in young people who were diagnosed with and treated for GD in childhood, QoL was found to be lower than in healthy controls, especially in the psychosocial domain. Although more research on this topic is needed, it emphasizes the need for additional support for young people with GD, both at school and from a psychological perspective (98).

This ETA guideline provides new recommendations for the management of pediatric GD including a longer phase of initial medical/ATD treatment, preference for DT instead of BR in most cases, complete thyroid gland ablation with personalized dose determination when using RAI and

involvement of a pediatric endocrinologist in all cases.

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