

Original Article

Guidelines for the treatment of childhood-onset Graves' disease in Japan, 2016

The Committee on Pharmaceutical Affairs, Japanese Society for Pediatric Endocrinology, and the Pediatric Thyroid Disease Committee, Japan Thyroid Association (Taskforce for the Revision of the Guidelines for the Treatment of Childhood-Onset Graves' Disease),

Kanshi Minamitani¹, Hirokazu Sato², Hidemi Ohye³, Shohei Harada⁴, and Osamu Arisaka⁵

¹*Department of Pediatrics, Teikyo University Chiba Medical Center, Chiba, Japan*

²*Sunrise Children's Clinic, Chiba, Japan*

³*Department of Internal Medicine, Ito Hospital, Tokyo, Japan*

⁴*Division of Neonatal Screening, National Center for Child Health and Development, Tokyo, Japan*

⁵*Department of Pediatrics, Dokkyo Medical University, Tochigi, Japan.*

Abstract. Purpose behind developing these guidelines: Over one decade ago, the “Guidelines for the Treatment of Graves' Disease with Antithyroid Drug, 2006” (Japan Thyroid Association (JTA)) were published as the standard drug therapy protocol for Graves' disease. The “Guidelines for the Treatment of Childhood-Onset Graves' Disease with Antithyroid Drug in Japan, 2008” were published to provide guidance on the treatment of pediatric patients. Based on new evidence, a revised version of the “Guidelines for the Treatment of Graves' Disease with Antithyroid Drug, 2006” (JTA) was published in 2011, combined with the “Handbook of Radioiodine Therapy for Graves' Disease 2007” (JTA). Subsequently, newer findings on pediatric Graves' disease have been reported. Propylthiouracil (PTU)-induced serious hepatopathy is an important problem in pediatric patients. The American Thyroid Association's guidelines suggest that, in principle, physicians must not administer PTU to children. On the other hand, the “Guidelines for the Treatment of Graves' Disease with Antithyroid Drug, 2011” (JTA) state that radioiodine therapy is no longer considered a “fundamental contraindication” in children. Therefore, the “Guidelines for the Treatment of Childhood-Onset Graves' Disease with Antithyroid Drug in Japan, 2008” required revision.

Key words: Graves' disease, guidelines, treatment

Received: October 3, 2016

Accepted: December 2, 2016

Corresponding author: Dr. Kanshi Minamitani, Department of Pediatrics, Teikyo University Chiba Medical Center, 3426-3 Anesaki, Ichihara-shi, Chiba 299-0111, Japan

E-mail: kminami@med.teikyo-u.ac.jp

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives (by-nc-nd) License <<https://creativecommons.org/licenses/by-nc-nd/4.0/>>.

Introduction

Graves' disease is defined as acquired autoimmune hyperthyroidism with a diffuse goiter. Graves' disease is a common disorder in adults, with a prevalence of approximately 0.5–1% (1, 2). It is often diagnosed and treated by general practitioners. The evidence-based “Guidelines for the Treatment of Graves' Disease

with Antithyroid Drug in Japan, 2006" (Japan Thyroid Association: JTA) (3) were prepared as the standard therapeutic protocol for Graves' disease for general physicians.

The majority of childhood hyperthyroidism cases are attributable to Graves' disease. Pediatric patients account for less than 5% of the total number of patients with Graves' disease and the prevalence in children is 0.02% (4, 5). Therefore, very few large cohort clinical studies have been conducted, and scientific evidence on childhood Graves' disease is scarce. Physicians must make diagnoses based on the "Guidelines for the Diagnosis of Graves' Disease" (6). However, these guidelines include very little information on pediatric treatment for Graves' disease. However, the guidelines do state that, "the remission rate with antithyroid drugs is lower in children with Graves' Disease, and the drug therapy is not always easy. Insufficient treatment of pediatric Graves' disease may result in major problems, and pediatric patients with Graves' disease should generally be treated by specialists" (3). Consequently, both the Committee on Pharmaceutical Affairs of the Japanese Society for Pediatric Endocrinology (JSPE) and the Pediatric Thyroid Diseases Committee of the JTA took action. These two groups conducted questionnaire surveys (7) and retrospective clinical studies, as well as comprehensive literature searches for preparation of the "Guidelines for the Treatment of Childhood-Onset Graves' Disease with Antithyroid Drug in Japan, 2008" (JSPE, JTA) (8).

Based on newer evidence, the "Guidelines for the Treatment of Graves' Disease with Antithyroid Drug in Japan, 2006" were also revised and combined with the "Handbook of Radioiodine (^{131}I) Therapy for Graves' Disease in Japan, 2007" (JTA) (9); subsequently, the "Guidelines for the Treatment of Graves' Disease in Japan, 2011" (JTA) (10) was published.

Since then, even newer findings on pediatric Graves' disease have been reported. One major problem faced by pediatric patients is the

occurrence of serious hepatopathy associated with PTU administration (11–18). According to the US guidelines, "Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of American Thyroid Association (ATA) and American Association of Clinical Endocrinologists" (19), it is suggested in principle that physicians refrain from using PTU in children. In addition, according to the "Guidelines for the Treatment of Graves' Disease in Japan, 2011" (10), radioiodine (^{131}I) therapy is no longer considered a "fundamental contraindication." In other words, ^{131}I is not contraindicated in children and is instead subject to "careful administration" (i.e., ^{131}I should be administered to children with care). This change has provided physicians with more therapeutic options (10). The current ATA guidelines recommend a lower initial dose of methimazole (MMI) (or thiamazole in Japan) than older guidelines (19). Newly reported findings in Japan include the efficacy of MMI and PTU in pediatric patients, as well as adverse reactions (20), the relationship between the initial MMI dose and effectiveness (21), the initial MMI dose and adverse reactions (22), and a higher remission rate with long-term MMI treatment (23).

Given these new findings and overseas reports, we revised the "Guidelines for the Treatment of Childhood-Onset Graves' Disease with Antithyroid Drug in Japan, 2008". These guidelines include statements of recommendation. For each recommendation, a "grade" and "level of the quality of the evidence" are provided. The "grade" indicates the strength of a recommendation, and the "level of the quality of the evidence" defines the level of the study used as the rationale for the recommendation. Recommendation grading was primarily based on published research findings. However, opinions from experts were provided if appropriate or in the absence of sufficient published findings.

Grade levels

1. Strong recommendation: "The recommendation

is beneficial for most patients.”

2. Weak recommendation: “In many cases, the recommendation is beneficial for patients; therefore, using the recommendation should be considered. Always make the most beneficial choice for the patient depending on circumstances”.

Level of the quality of the evidence

- Low: Uncontrolled case collection
- Moderate: Uncontrolled cohort study
- High: Controlled cohort study, non-randomized controlled trial

Evidence that has not been investigated, but is widely acknowledged is labeled “consensus.”

1. Definition and Diagnosis of Graves' Disease

Recommendation

- 1-1. Graves' disease is an autoimmune disease. Thyroid stimulating hormone (TSH; thyrotropin) receptor antibodies (i.e., thyrotropin receptor antibodies [TRAb]) stimulate the TSH receptor, leading to increased thyroid hormone production and secretion, causing diffuse toxic goiter. 1 (Consensus)
- 1-2. Hyperthyroidism, defined as the increased production and secretion of thyroid hormone, and an excess of thyroid hormone in the absence of increased thyroid hormone production are collectively called thyrotoxicosis. 1 (Consensus)

Explanation

The term thyrotoxicosis refers to “a clinical state that results from increased metabolism and activity due to an excess of thyroid hormone”. Therefore, thyrotoxicosis is not a synonym for hyperthyroidism. Hyperthyroidism, defined as the increased production and secretion of thyroid hormone, and an excess of thyroid hormone (i.e., excess intake of thyroid hormone and destructive thyroiditis, defined as a leakage of thyroid hormone caused by inflammatory destruction

of thyroid follicles) in the absence of increased thyroid hormone production are collectively called thyrotoxicosis (1, 2).

Hyperthyroidism is a disorder characterized by excessive thyroid hormone secretion. In addition to Graves' disease, hyperthyroidism has multiple causes, including a TSH-producing tumor, choriocarcinoma, struma ovarii, toxic multinodular goiter (TMNG), toxic adenoma (TA), congenital hyperthyroidism (gain-of-function mutation of the TSH receptor or G protein), and excessive iodine.

Common causes of destructive thyroiditis include painless thyroiditis, subacute thyroiditis, acute suppurative thyroiditis, radiation thyroiditis, and drug-induced thyrotoxicosis. Amiodarone, gonadotropin releasing hormone derivatives, lithium carbonate, or interferon-alpha may cause Graves' disease or destructive thyroiditis.

The majority of pediatric thyrotoxicosis cases involve hyperthyroidism, and most of these patients develop Graves' disease (4, 5). In contrast, subacute thyroiditis is extremely rare in children.

Graves' disease was named after the Irish physician Robert Graves, who studied and reported this disease. This term is usually used in English-speaking countries. In non-English-speaking countries, the term Basedow's disease, named after a German physician, Karl Adolph von Basedow, is more commonly used.

2. Diagnosis of Graves' Disease

Recommendation

- 2-1. A diagnosis of Graves' disease should be based on the “Guideline for the Diagnosis of Graves' Disease (revised on June 24, 2013)” (Table 1), which was prepared by the JTA and is available on their website. 1 (Consensus)
 - a) Clinical findings
 1. Signs of thyrotoxicosis such as tachycardia, weight loss, finger tremor, and sweating.

Table 1. Guidelines for the diagnosis of Graves' disease (Japan Thyroid Association)

-
- a) Clinical findings
1. Signs of thyrotoxicosis such as tachycardia, weight loss, finger tremor, and sweating.
 2. Diffuse enlargement of the thyroid gland.
 3. Exophthalmos and/or specific ophthalmopathy.
- b) Laboratory findings
1. Elevation in serum free thyroxine (FT4) and/or free triiodothyronine (FT3) level.
 2. Suppression of serum thyroid stimulating hormone (TSH): less than 0.1 μ U/ml.
 3. Positive for anti-TSH receptor antibody (TRAb or TBII) or thyroid stimulating antibody (TSAb).
 4. Elevated radioactive iodine (or $^{99m}\text{TcO}_4^-$) uptake to the thyroid gland.
- 1) A patient is diagnosed with Graves' disease if he/she has satisfied at least 1 of the clinical findings and all 4 laboratory findings.
 - 2) A patient is suspected of having Graves' disease if he/she has satisfied at least 1 of the clinical findings and laboratory findings 1–3.
 - 3) A patient is suspected of having Graves' disease if he/she has satisfied at least 1 of the clinical findings and both of laboratory findings 1–2. Elevation in serum FT4 has usually been present for at least 3 months.

【Notes】

1. Decrease of serum cholesterol and increase of serum alkaline phosphatase are often observed.
 2. There are rare cases with free triiodothyronine (FT3) elevation alone and normal FT4.
 3. A patient is diagnosed with "euthyroid Graves' disease" or "euthyroid ophthalmopathy" if he/she has ophthalmopathy and is positive for TRAb or TSAb, but shows normal FT4 and TSH.
 4. In an elderly patient, clinical symptoms and signs including an enlargement of the thyroid gland, may not be clear.
 5. In children, decreased scholastic ability, accelerated growth, restlessness, and other symptoms may be observed.
 6. The FT3/FT4 ratio is helpful to exclude painless thyroiditis.
 7. Measurements of thyroid blood flow and urinary iodine levels are useful for differentiation of painless thyroiditis.
-

Revised on June 24, 2013.

2. Diffuse enlargement of the thyroid gland.
 3. Exophthalmos and/or specific ophthalmopathy.
- b) Laboratory findings
1. Elevation in serum free thyroxine (FT4) and/or free triiodothyronine (FT3) level.
 2. Suppression of serum thyroid stimulating hormone (TSH): less than 0.1 μ U/mL.
 3. Positive for anti-TSH receptor antibody (TRAb or TSH binding inhibitory immunoglobulin (TBII)) or thyroid stimulating antibody (TSAb).
 4. Elevated radioactive iodine (or $^{99m}\text{TcO}_4^-$) uptake to the thyroid gland.
- 1) A patient is diagnosed with Graves' disease if he/she has satisfied at least 1 of the clinical findings and all 4 laboratory findings.
 - 2) A patient is suspected of having Graves' disease if he/she has satisfied at least 1 of the clinical findings and laboratory findings 1 through 3.
 - 3) A patient is suspected of having Graves' disease if he/she has satisfied at least 1 of the clinical findings and both of laboratory findings 1 and 2. Elevation in serum FT4 has usually been present for at least 3 months.
- 2-2. A Graves' disease severity assessment should be based on the following criteria:
- (1) Clinical assessment of the symptoms of thyrotoxicosis (goiter size).
 - (2) Pre-treatment serum FT4 level analysis (e.g. Severe: ≥ 7 ng/dL, Moderate: $< 5-7$ ng/dL, Mild: < 5 ng/dL) (FT4 levels may vary depending on the measurement kit. The above values are merely references).
 - (3) Ultrasonography findings.
- The assessment of criteria (1) through (3) should be performed in a comprehensive manner. 1 (●○○)

Explanation

1. Diagnosis

The "Guidelines for the Diagnosis of Graves' Disease, 2013" (6) were prepared for adult patients primarily; however, these guidelines should also be used to diagnose pediatric patients. Diagnosis of Graves' disease can be confirmed in a patient who has, according to clinical observations, the following: (1) symptoms of thyrotoxicosis, including tachycardia, (2) diffuse goiter, and (3) distinctive ocular manifestations. Additionally, laboratory findings will show the following: (1) high FT4 or FT3 level, (2) suppressed TSH, (3) causative positive TSH receptor antibodies (TRAb, TBII, TSAbs), and (4) nuclear medicine findings of a high uptake rate in the thyroid gland. However, few medical institutions can perform thyroid uptake and scintigraphy tests. These tests are not always performed, even on adults. Therefore, treatment can be initiated with a diagnosis of "probable Graves' disease". In pediatric patients, radiation exposure should be kept to a minimum. Such tests should be performed only in cases involving difficult diagnoses. In recent years, measurement of thyroid blood flow by ultrasonic pulse Doppler has been widely used for the diagnosis of Graves' disease.

Graves' disease is extremely rare in children 5 years or younger. The occurrence of Graves' disease increases from age 11 to 15 yr, with a peak at high-school age (2, 4). A hospital-based study of 132 children with Graves' disease 15 yr or younger in Japan, found that only 4 patients were under 5 yr-of-age (24). However, a few cases of Graves' disease development in very young children (1–2 yr) have been reported. Therefore, careful observation is necessary, regardless of age. Graves' disease is more common in girls, with reported boy to girl ratios of around 1:3 to 1:6 (2, 4).

The major clinical symptoms of pediatric Graves' disease are goiter (68.4%), excessive sweating (53.4%), fatigue (50.4%), restlessness (47.4%), and finger tremors (45.1%).

Table 2. Clinical symptoms and their frequencies in pediatric Basedow's disease

Goiter	68.40%
Excessive sweating	53.40%
Fatigue	50.40%
Restlessness	47.40%
Hand tremor	45.10%
Exophthalmos	38.30%
Weight loss	36.10%
Increased appetite	35.30%
Tachycardia	33.80%
Palpitation	24.80%
Decreased academic performance	24.10%
Decreased athletic performance	15.00%
Sensitivity to heat	12.00%
Increased bowel movement	11.30%
Slight fever	10.50%
Others: insomnia, thirst, bed-wetting, amenorrhea	

Sato H. *J Pediatr Endocrinol Metab* 2014; 27: 677–83 (24).

Exophthalmos (38.3%), weight loss (36.1%), and tachycardia (33.8%) are also common (24) (Table 2). In adults, frequent clinical symptoms include goiter (69%), ocular manifestations (63%), weight loss (61%), sensitivity to heat (55%), finger tremors (54%), and palpitations (51%) (25). Weight loss is less common in children. Weight gain is a common physiologic change in puberty. Therefore, a lack of weight gain in an adolescent is a significant clinical observation. It is difficult to recognize finger tremors in schoolchildren, whereas hyperactivity, typified by restlessness, and excessive growth promotion tend to be easily recognized. Occasionally, the drawing of a pediatric growth curve might help to detect the onset of the disease. Fatigue is a common symptom among patients who are junior high-school students. Other nonspecific symptoms, although less frequent, have been reported; these include a decline in academic performance, slight fever, nocturnal enuresis, menstrual irregularities, and diarrhea. In addition, thyrotoxic myopathy (muscle weakness), caused by increased catabolism of muscle fibers, has been reported to precede thyrotoxicosis in

two-thirds of studied patients (26). Thyrotoxic myopathy is occasionally accompanied by thyrotoxic hypokalemic periodic paralysis or encephalopathy associated with thyroid storm.

Patients may complain of discomfort due to tachycardia, palpitations, dyspnea, cardiac dilatation, or cardiac failure. However, atrial fibrillation is rare in children. An apical systolic regurgitant murmur may be present because of mitral valve insufficiency resulting from papillary muscle dysfunction (4).

Prepubertal patients with Graves' disease exhibit nonspecific physical symptoms, and may manifest various mental symptoms. Accordingly, the disease tends to be overlooked and 6 to 12 mo may easily pass between onset of the disease and the final diagnosis. Therefore, when a school-age patient visits a hospital, clinical data tend to indicate a severe condition and accelerated growth and an increased bone age may be observed. However, this rapid growth will not affect the final height of the patient (27–29).

The reported frequencies of exophthalmos in children are almost similar to those in adults; however, this symptom is minor, and highly active ophthalmopathies such as ocular motility disorder or optic nerve disturbances are fairly uncommon (30, 31).

The incidence of Graves' disease in a sibling of the index case is 11.6-fold higher than that in the general population (32). The incidence of Graves' disease in identical twins is significantly higher (35%) than in dizygotic twins (3%). As reported, 79% of the pathogenic mechanisms of Graves' disease can be explained by genetic factors (33). In Japan, 40% of children with Graves' disease have a familial history of the disease (24), and the frequency of familial Graves' disease is 2–3% (4). In addition to multiple genetic factors, environmental factors are involved; when a patient's immune tolerance to thyroid antigens is broken, they will develop Graves' disease. Several candidate gene analyses and comprehensive genome-wide association studies have identified the following disease-

susceptibility genes: *human leukocyte antigen (HLA)-DR3*, *HLA-DRβ1-Arg74*, *thyroglobulin (Tg)*, *TSH receptor*, *cytotoxic T-lymphocyte-associated protein 4 (CTLA4)*, *CD40*, *protein tyrosine phosphatase-22 (PTPN22)*, *zinc-finger gene in AITD susceptibility region (ZAF1)*, *Fc receptor-like 3 (FCRL3)*, *interleukin-23 (IL-23R)*, *interferon-induced helicase 1 (IFIH1)*, *Forkhead box P3 (FOXP3)*, and *interleukin-2 receptor-α (IL-2RA; CD25)*, among others (34, 35). Notably, HLA regions are attributed to 20% of the genetic factors associated with Graves' disease, and only SNPs in the *CTLA4* and *TSH receptor* genes have odds ratios greater than 2 (36, 37). The following environmental factors have been reported to cause Graves' disease: infectious diseases, iodine, smoking, alcohol, stress, pregnancy/childbirth, selenium, drugs, dioxins such as polychlorinated biphenyls (PCBs), and radiation exposure (38).

The function of the thyroid gland changes according to the patient's age, sex, and secondary sexual characteristics. Therefore, it is not appropriate to apply adult standards to children. Previously, the reference values for children were based on solid-phase radioimmunoassay (RIA) standards that were established by the Research Group on Reference Values for Children and presented in the "Reference Values for Laboratory Tests on Japanese Children" (published in 1996 by the Japan Public Health Association). Several non-RIA methods have been developed since these standards were established. Presently, an enzyme immunoassay (EIA), that does not use radioactive substances, and a more sensitive luminescent immunoassay (LIA) are commonly used. In particular, fully automatic measuring devices have been developed for a chemiluminescent enzyme immunoassay (CLEIA) and chemiluminescent immunoassay (CLIA). Reference values of thyroid function in healthy children can be measured by a kit, ECLusys® (Roche Diagnostics GmbH, Mannheim, Germany) with an electrochemiluminescent immunoassay (ECLIA) (39) (Table 3). According to these standards, the maximum FT3 value is

Table 3. Reference levels of FT3, FT4, and TSH by age (ECLIA method)

Age group	FT3 (pg/mL)	FT4 (ng/dL)	TSH (μ U/mL)
4–6 yr	2.91–4.70	1.12–1.67	0.62–4.90
7–8 yr	3.10–5.10	1.07–1.61	0.53–5.16
9–10 yr	3.10–4.87	0.96–1.60	0.67–4.52
11–12 yr	2.78–4.90	1.02–1.52	0.62–3.36
13–14 yr	2.77–4.59	0.96–1.52	0.54–2.78
15 yr	2.50–4.64	0.85–1.53	0.32–3.00
Adult	2.20–4.30	0.80–1.60	0.20–4.50

Iwaku K. *Endocr J* 2013; 60: 799-804 (38).

5.10 pg/mL (age 7–8 yr), and the maximum FT4 value is 1.67 ng/dL (age 4–6 yr). However, values may vary depending on the measurement kit.

Increased serum alkaline phosphatase levels in patients with Graves' disease are noted in the JTA's diagnostic guidelines. However, age-dependent reference values in healthy children show a large range compared to the range of adult values. So, alkaline phosphatase levels have been deleted as a diagnostic reference note in these guidelines.

In the JTA's diagnostic guidelines, measurements of "thyroid blood flow" and "urinary iodine" are noted. A maximum blood flow rate of the superior thyroid artery on ultrasonic pulse Doppler that exceeds 45 cm/sec supports a diagnosis of Graves' disease (40). Additionally, a ratio of 0.5 or more between blood flow pixels/total pixels as measured by a semi-quantitative method is a diagnostic indicator for Graves' disease (41). In patients with Graves' disease, iodine uptake of the thyroid gland increases and urinary iodine excretion decreases. On the contrary, in patients with painless thyroiditis, iodine uptake of the thyroid decreases and urinary iodine excretion increases as a result of thyroid gland destruction. A $100 \times$ TRAb/total urinary iodine ratio of over 3:0 supports a diagnosis for Graves' disease (42).

2. Severity

Poor remission rates are reported in Graves'

disease patients with high levels of FT4 and FT3, with large goiter, with T3 pre-dominance, or with childhood onset (1, 2, 43).

The "Guidelines for the Treatment of Graves' Disease, 2011" suggest that the starting dose of antithyroid drug be modified according to the severity of the disease (10). According to the ATA guidelines, severe Graves' disease is defined as a FT4 level 2–3 times greater than the upper limit of the reference value (19). According to a retrospective study of pediatric Graves' disease in Japan, in which MMI was used as the initial treatment, the mean pre-treatment FT4 level of patients initially treated with a high dose of MMI was 6.1 ± 2.0 ng/dL. On the other hand, the pre-treatment FT4 level of patients initially treated with a low dose of MMI was 4.6 ± 2.6 ng/dL (21). It is recommended that the pre-treatment FT4 level be used as a reference guide for assessing the severity of the disease and predicting the therapeutic effect.

Graves' disease is directly induced by TRAb, and the TRAb level is therefore useful as a diagnostic or control index. However, the disease prognosis cannot be predicted from the pre-treatment TRAb value (10, 44).

A previous report indicated that the MMI requirement at 1 year after starting treatment is greater if the maximum blood flow rate in the inferior thyroid artery exceeds 100 cm/sec at disease onset; ultrasonic measurement of the maximum blood flow rate might predict responsiveness to an antithyroid drug (45).

3. Initial Treatment of Graves' Disease

Recommendation

3-1. If a patient with Graves' disease does not have a history of treatment, explain the various treatment options, including antithyroid drug therapy, surgical treatment, and radioiodine therapy (^{131}I therapy) before initiating treatment. Thoroughly explain the benefits and drawbacks of each treatment option, as well as the indications and

contraindications, and obtain consent from the patient and their family before selecting a treatment method. 1 (Consensus)

- 3-2. The benefits of antithyroid drugs include no risk of radioactive iodine exposure, no bothersome hospitalization, and no surgical procedure. The drawbacks include a lower remission rate in children compared to adults, treatment-related suffering, longer duration of the treatment, and higher frequency of adverse drug reactions. 1 (Consensus)
- 3-3. Surgical treatment is more reliable and associated with a shorter treatment duration. However, surgery requires invasive procedures, and thyroid hormone replacement therapy will be required after the surgery. To avoid recurrence, total or near total thyroidectomy to reduce the remaining thyroid tissue should be performed. Either surgery must be performed by a skillful thyroid surgeon. 1 (Consensus)
- 3-4. ¹³¹I therapy is a safe and reliable treatment. However, this treatment is associated with a high risk of future hypothyroidism development. In Japan, ¹³¹I therapy is subject to "careful administration" for children 18 yr or younger because of the risk of thyroid cancer development or gonadal damage consequent to radiation exposure. 1 (Consensus)
- 3-5. For children, antithyroid drug therapy is the primary treatment option. 1 (Consensus)

Explanation

Multiple treatment options are available for Graves' disease, including antithyroid drug therapy, surgical treatment, and ¹³¹I therapy (46, 47). Drug therapy is available on an outpatient basis, and can be used by most patients with Graves' disease. In Japan, approximately 90% of patients without a treatment history are initially treated with antithyroid drugs. Similarly, long-term antithyroid drug treatment tends to be used in Europe (approximately 80%), Asia and

Oceania, and South America (48). Previously, more than 70% of patients without a treatment history in the US received ¹³¹I therapy. However, in recent years, 40% of patients without a treatment history are initially treated with antithyroid drugs; thus, the use of ¹³¹I therapy is decreasing (48, 49).

The indications for surgical treatment for Graves' disease are limited to patients who wish to achieve remission sooner, have large goiters, have complicating thyroid cancer, do not wish to receive treatment with antithyroid drugs, or cannot use antithyroid drugs (1, 2, 10, 19). If a patient exhibits severe symptoms of thyrotoxicosis, antithyroid drugs should be used initially to normalize thyroid gland function before undergoing surgical treatment.

As a general rule, in Japan, ¹³¹I therapy is subject to "careful administration" for children 18 yr or younger. However, there is no evidence to support this designation. ¹³¹I therapy is only used for patients who do not wish to take antithyroid drugs or receive surgical treatment or who cannot choose other treatment options (10). However, the ATA guidelines suggest that ¹³¹I therapy be considered at an early stage for pediatric patients 5 yr or older with severe Graves' disease who do not achieve remission via drug therapies or fail to achieve remission with drug therapies after 1 or 2 yr (19). If the patient exhibits severe symptoms of thyrotoxicosis, antithyroid drug therapy should be combined with a β -blocker to improve the systemic condition and ensure that ¹³¹I therapy can be performed safely.

For the above reasons, antithyroid drug therapy is the primary treatment option for pediatric patients (8, 10, 50–52).

4. Drug Therapies for Graves' Disease

Recommendation

- 4-1. As a general rule, use an antithyroid drug therapy for Graves' disease. 1 (Consensus)
- 4-2. Two antithyroid drugs are available: Thiamazole [MMI, proprietary name:

Mercazole Tablet 5 mg, Thiamazole Tablet 5 mg] and Propylthiouracil [PTU, proprietary name: Thiuragyl Tablet 50 mg, Propacil Tablet 50 mg]. Use MMI as the first-line therapy. If using PTU for pediatric Graves' disease, thoroughly explain that the patient may develop severe hepatic dysfunction as an adverse effect and administer the drug cautiously upon obtaining consent. 1 (●●○)

- 4-3. The starting dose of MMI should be 0.2–0.5 mg/kg/d once daily (QD) or twice daily (BID); the starting dose of PTU should be 2–7.5 mg/kg/d three times daily (TID). When a dose for a pediatric patient (calculated based on his/her body weight) exceeds the dose for adults, use the adult dose as a general rule (15 mg/d for MMI, 300 mg/d for PTU). For severe cases, use twice the amount of the maximum dose. 1 (●●○)
- 4-4. For a patient with severe symptoms of thyrotoxicosis, use a β -blocker concurrently. 2 (Consensus)
- 4-5. After initiating treatment, monitor adverse drug reactions every 2–3 wk for at least 2–3 mo. Perform blood and urine tests in addition to the thyroid function test. 1 (●●○)

Explanation

1. Choosing an antithyroid drug

Two types of antithyroid drugs, propylthiouracil (PTU) and thiamazole, are available. Thiamazole comprises 2 subtypes of drugs, MMI and carbimazole (CBZ). Methimazole is mainly used in Japan and the US, and CBZ is used in Europe. Carbimazole is promptly and completely metabolized to MMI in the liver. However, because the side chain is detached, 10 mg of CBZ is equivalent to 6 mg of MMI. Both PTU and MMI inhibit thyroid peroxidase and suppress iodination of tyrosyl residues on TG (inhibition of organification). In addition, PTU and MMI inhibit TG synthesis, coupling two iodotyrosines to form T3 or T4, and the secretion of thyroid hormone (53). PTU inhibits a Type-I deiodination enzyme in the liver and

peripheral tissues and suppresses the conversion from T4 to T3. Therefore, PTU is considered for patients with thyroid storm. However, the clinical response is unsatisfactory unless a large quantity (approximately 1,000 mg of PTU) is used (54). The reported potency of MMI is 10- to 100-fold greater than that of PTU (55). The serum half-life of MMI is between 6 and 8 h, whereas that of PTU is 0.5 h. Therefore, MMI can be administered only once daily, whereas PTU must be administered 3 times daily (56). MMI and PTU do not differ with respect to placental transportability. MMI exhibits low protein-binding activity and a milk/plasma (m/p) concentration ratio of approximately 1. In contrast, PTU exhibits high serum protein-binding activity, and a relatively small amount of PTU is excreted into milk (m/p ratio: approximately 0.1) (10).

Compared with PTU, MMI is preferred in Japan and Europe because of its once-daily dosing regimen. Such a regimen allows more rapid normalization of thyroid function with MMI than with PTU (57). In addition, MMI causes fewer adverse drug reactions. Accordingly, MMI is preferred in those areas (Japan: approximately 85% of cases, Europe: approximately 95% of cases) (7, 49). However, in the US, PTU was initially less expensive than MMI and was used predominantly in the 1980s (approximately: 85% of cases) (49). In the late 1990s, the first generic MMI formulations were released and use of MMI has increased (58).

In comparison with MMI, PTU is associated with a higher incidence of serious adverse drug reactions (59–62). In particular, many cases of severe hepatopathy, liver failure (11–18), and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis syndrome (63–66) have been reported in children. In the US, many cases of serious PTU-associated hepatic dysfunction have been reported in children younger than 17 years. Regarding MMI, an association between use in early pregnancy and teratogenicity (i.e., MMI embryopathy) has been suggested (53, 67, 68). Based on these findings, the ATA guidelines

principally suggest use of MMI for antithyroid drug therapy, whereas use of PTU is limited to the following exceptions: (1) during the first trimester of pregnancy, (2) patients with thyroid storm, and (3) patients with minor reactions to MMI who refuse ^{131}I therapy or surgery (10, 19). In Japan, the incidence of PTU-associated severe hepatopathy is extremely rare in children with Graves' disease. However, given the reported situation in the US, these guidelines suggest that physicians provide a sufficient explanation to patients and families and obtain consent before administering PTU.

A retrospective study of children who developed Graves' disease at 15 yr or younger was conducted to evaluate the interval from treatment initiation to normalization of thyroid function, and the frequency of adverse drug reactions relative to the type and dosage of the initial medication. In this study, 133 children with Graves' disease who had been monitored for more than 1 yr after the start of antithyroid drug therapy were divided into 4 groups: MMI Low-Dose Group (low MMI group: initial dose < 0.75 mg/kg, $n = 34$), MMI High-Dose Group (high MMI group: $\text{MMI} \geq 0.75$ mg/kg, $n = 30$), PTU Low-Dose Group (low PTU group: $\text{PTU} < 7.5$ mg/kg, $n = 24$), and PTU High-Dose Group (high PTU group: $\text{PTU} \geq 7.5$ mg/kg, $n = 45$). The mean intervals to normalization of thyroid function were 1.9 mo in the low MMI group, 1.4 mo in the high MMI group, 3.1 mo in the low PTU group, and 1.7 mo in the high PTU group. The low PTU group had a significantly longer treatment to normalization interval. However, a between-group comparison showed no significant relationships between the pre-treatment FT4 level and the interval to normalization of thyroid function (20).

2. Starting doses and dosage regimens of antithyroid drugs

Since the recent designation of a reduction in adverse drug reactions as the highest priority, doses of antithyroid drugs have tended to

decrease. As a textbook example, the stated starting doses are 0.25–1.0 mg/kg/d for MMI (2, 4) and 2–6 mg/kg/d for PTU (5). This amount is equivalent to 5–15 mg/d of MMI in adults.

The "Guidelines for the Treatment of Graves' disease in Japan, 2011" suggest starting doses of MMI of 15 mg/d for mild and moderate cases and 30 mg/d for severe cases. The suggested starting dose of PTU is 300 mg/d.

According to the ATA guidelines (19), the suggested starting dose of MMI is 0.2–0.5 mg/kg/d, and MMI should be used within a range of 0.1–1.0 mg/kg/d (27, 44, 50, 69–72). Specifically, the suggested doses are 1.25 mg/d for infants, 2.5–5.0 mg/d for children aged 1–5 yr, 5–10 mg/d for children aged 5–10 yr, and 10–20 mg/d (i.e., the adult dose) for children and adolescents aged 10–18 yr. For severe cases, the dose can be increased to as high as twice the above-listed amounts. According to the guidelines used in Brazil (73), the suggested dose of MMI is 0.2–0.5 mg/kg/d, and MMI should be used within a range of 0.1–1.0 mg/kg/d. The upper limits are 30 mg/d for MMI. The suggested dose of PTU is 4.7–8.6 mg/kg/d. In a review article by Kaguelidou (74), the initial starting dose of MMI was 0.5–1.0 mg/kg/d with a maximum of 30 mg/d, whereas that of PTU was 5–10 mg/kg/d with a maximum of 300 mg/d. A retrospective study reported MMI starting doses of 0.7 mg/kg/d for children younger than 7 yr and 0.5 mg/kg/d for children older than 7 yr. In this study, an average of approximately 6 mo was required for patients younger than 7 yr to achieve normalization of thyroid function (75). In another study, low-dose MMI treatment was found to be successful for mild cases; however, for severe cases, dose increases only led to an increase in the incidence of adverse drug reactions, and the efficacy did not differ from that of low-dose treatment for mild cases. Based on these results, this study suggested a standard MMI dose of 0.5 mg/kg/d. This amount could be adjusted depending on disease severity. In particular, the suggested doses are 2.5–10 mg/d for children younger than 4 yr, 10–20 mg/d for

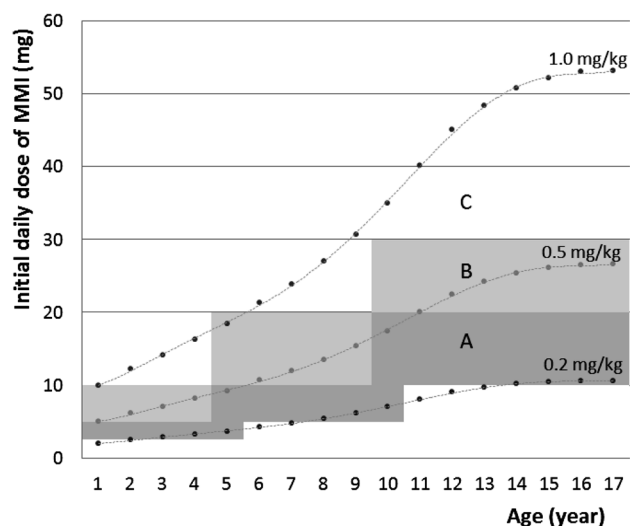


Fig. 1. Initial Methimazole (MMI) dose by age. The curve shows the doses per weight calculated from the average weights of Japanese female children. Low-dose group (Group A): Doses by age recommended in the US guidelines. High-dose group (Group B): Doses higher than but less than 2-fold that of Group A and lower than 30 mg/d (recommended for severe cases in the Japanese Guidelines for adults). Super high-dose group (Group C): Doses higher than that of Group B (Sato H. *J Pediatr Endcr Met* 2012; 25: 863-7) (21).

children between 4–10 yr of age, and 15–30 mg/d for children 10 yr or older (Fig. 1) (21).

Specialists have expressed differing opinions on whether to increase the doses for childhood-onset cases according to disease severity. Thyroidologists (internal medicine physicians) tend to use lower doses than do pediatric endocrinologists (pediatricians) (7). For adults, the highest priority is placed on reducing the incidence of adverse drug reactions, and physicians thus tend to initiate treatment with smaller doses of MMI than those used previously (19). In addition, the concurrent use of inorganic iodine is thought to reduce the required dose of MMI.

A young age, large goiter, elevated pre-treatment FT4 level, and persistently high TRAb level at the initial visit have been reported as

predictors of poor prognosis (i.e., decreased remission rate) (76–79). Using these findings as a reference and considering the impact of increased thyroid function on a patient's growth, an initial dose of 1 mg/kg/d of MMI is considered reasonable for thyroid function normalization in severe cases with symptoms of heart failure. For mild and moderate cases, and particularly for older children, a starting dose of approximately 0.5 mg/kg/d of MMI is suggested. If the FT4 level does not decrease as expected with an initial low-dose treatment, the dose can be increased.

Pediatric doses calculated based on body weight may occasionally exceed the recommended doses for adults. However, the use of a larger dose of MMI will only increase the incidence of adverse drug reactions; it will not affect the effectiveness of the therapy. Therefore, these guidelines suggest that the recommended pediatric dose must not exceed the adult dose. If symptoms cannot be controlled with the recommended dose of the antithyroid drug, the patient must be referred to a pediatric endocrinologist or thyroidologist.

Most adverse reactions to antithyroid drugs tend to emerge within 3 mo after treatment initiation (59–61). As a general rule, the patient should be monitored for adverse reactions every 2–3 wk for at least the first 3 mo. In particular, monitoring should be performed every 2 wk during the first 2 mo. Adverse drug reactions may occur even during maintenance therapy; therefore, the patient must be monitored at prescribed intervals. For monitoring, the complete blood count, differential white blood count, and levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ -GTP), and total bilirubin (T-Bil) should be checked. (80–82). The frequency of adverse reactions to MMI is associated with the delivered dose (21, 62, 83–85).

3. Combination therapy

Thyroid hormone affects the actions of catecholamines, thus causing the typical

symptoms of thyrotoxicosis, which include tachycardia, excess sweating, and restlessness. Concomitant use of β -blockers is useful for patients with severe symptoms of thyrotoxicosis. The ATA guidelines strongly suggest concomitant use of a β -blocker if pulse rate exceeds 100/min (19). The following β -blockers should be administered orally: propranolol, 0.5–2.0 mg/kg/d TID; atenolol, 1–2 mg/kg/d QD; metoprolol, 1.0–2.0 mg/kg/d TID; nadolol; or esmolol. These β -blockers can be used carefully by patients with bronchial asthma (86). In Japan, however, the use of β_1 -nonselective β -blockers (e.g., propranolol, nadolol) is contraindicated in patients with bronchial asthma.

4. Other drug therapies and combination therapies

Inorganic iodine can be used by patients who are unable to use antithyroid drugs. For infants or schoolchildren, the recommended starting doses are 10–20 mg /d QD of potassium iodide solution (adjusted dose of iodine: 12.5 mg/mL) or 3–4 drops/d of Lugol's solution (1 drop of Lugol's solution = 6.3 mg iodine). For junior high school students, 1–2 potassium iodide pills (inorganic iodine: 38.2 mg/pill) should be taken per day. A patient who intends to use potassium iodide must be referred to a thyroidologist as soon as possible.

A large amount of inorganic iodine will inhibit organification of iodine and suppress the release of thyroid hormone, thus promptly controlling the thyroid function (Wolff–Chaikoff effect). Inorganic iodine therapy should be used to control thyroid function in the case of thyroid storm, as pre-operative Graves' disease care, as pre- and post-¹³¹I therapy, or in a patient who has developed an adverse reaction and cannot use any antithyroid drugs (87). In such cases, careful consideration must be given to the potential for escape phenomenon, or a rapid exacerbation of thyrotoxicosis after treatment discontinuation. A study of adult patients with relatively small goiters, FT4 levels ≤ 2.5 ng/dL, and relatively low TRAb levels, showed that approximately two-

thirds of patients treated with inorganic iodine monotherapy did not develop escape phenomenon and maintained normal thyroid function for a long period; furthermore, approximately 60% of these patients achieved remission after an average of 7.4 yr of treatment (88, 89). In adults with Graves' disease, combined treatment with MMI and inorganic iodine was used to reduce the MMI dose (83, 90, 91). In these studies, this combination therapy reduced blood flow in the thyroid gland and bleeding during surgery; however, exacerbated thyroid gland enlargement was also reported. Only a few reports have discussed the use of combination therapy in pediatric patients; therefore, this therapy should be administered to children with caution (87).

For patients with thyroid function that is sensitive to changes in MMI dose and experience exacerbation of the condition, block and replace therapy is sometimes used to stabilize thyroid function. This therapy uses a sufficient amount of MMI (15 mg/d) to control thyroid function, combined with a minimum amount of L-thyroxine (LT4) to maintain normal thyroid function. Another type of block and replace therapy uses large fixed amounts of MMI and LT4. This therapy uses the immunosuppressive action of MMI to improve the remission rate. However, evidence that this type of long-term combination therapy improves the remission rate is not convincing, and this regimen was reported to significantly increase the incidence of adverse reactions. Therefore, the use of this therapy is not recommended (92–96).

Other drug therapies include lithium carbonate, perchlorate, corticosteroid, cholestyramine, or immunoregulation therapy (rituximab).

Lithium carbonate is taken up by the thyroid gland via active transport by the sodium/iodide symporter (NIS). This agent suppresses the synthesis and secretion of thyroid hormone, but causes escape phenomenon. Lithium carbonate is less effective than MMI and has been associated with many reported cases of adverse drug

reactions. This therapy is not covered by public health insurance.

Similarly, perchlorate (Perchloracap®) is also taken up by the thyroid gland via NIS-mediated active transport. This drug releases iodine in the thyroid gland and inhibits the NIS, thus suppressing thyroid hormone synthesis. Perchlorate is used to diagnose the type of congenital hypothyroidism. However, this agent has not been approved by the Ministry of Health, Labor and Welfare. Adverse effects of perchlorate treatment, such as fever, rash, enlarged lymph nodes, renal disorders, agranulocytosis, and critical aplastic anemia, have been reported. Currently, perchlorate is not commonly used for long-term treatment of Graves' disease.

When used in large doses, corticosteroid can suppress T4 secretion from the thyroid gland or conversion of T4 to T3 in peripheral tissues. However, to avoid serious side effects related to long-term use, corticosteroid use should be limited to treatment of thyroid storm, Graves' ophthalmopathy, or localized pretibial myxedema, or for pre-thyroidectomy control in patients with severe Graves' disease.

Cholestyramine, an anion exchange resin, binds both T4 and T3 and inhibits enterohepatic circulation. Cholestyramine may rapidly reduce the T3 and T4 levels when used concurrently with MMI for thyrotoxicosis (97). However, this treatment is not covered by health insurance.

Rituximab is an anti-CD20 monoclonal antibody, that specifically targets CD20-positive B lymphocytes via antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis induction. Rituximab has been reported to be effective for non-Hodgkin's lymphoma, granulomatosis with polyangiitis, rheumatoid arthritis, systemic lupus erythematosus, pediatric refractory nephrotic syndrome, idiopathic thrombocytopenic purpura, and type 1 diabetes mellitus. The ability of rituximab to reduce TRAb levels has been evaluated (98).

5. Method for Reducing Antithyroid Drug Doses, Maintenance Therapy, and Duration of Treatment

Recommendation

- 5-1. Once serum FT4 and FT3 levels have normalized, start reducing the antithyroid drug dose. 1 (Consensus)
- 5-2. Usually, the thyroid function will stabilize 2–3 mo after starting the medication; the standard maintenance dose ranges from 5 mg/every other day to 5 mg/d. 1 (●○○)
- 5-3. At least once every 3–4 mo, perform a thyroid function test and general blood test. While using PTU, urinalysis and annual myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) measurement are necessary to avoid overlooking signs of MPO-ANCA-associated vasculitis syndrome. 1 (●●○)
- 5-4. To achieve functional stabilization, small amounts of MMI and LT4 may be combined. 2 (Consensus)
- 5-5. For at least 18–24 mo, continue antithyroid drug therapy to maintain remission. 2 (●○○)
- 5-6. Long-term continuous antithyroid drug treatment (5–10 yr) may lead to remission. 1 (●●○)

Explanation

1. Management during treatment

Graves' disease may induce abnormalities in the hematopoietic system, immune system (79), or hepatic function (80, 81).

Most adverse reactions to antithyroid drugs tend to emerge within 3 mo of starting the medication. As a general rule, monitor the patient every 2–3 wk, at least during the first 3 mo, and check for any adverse reactions. In particular, monitoring should be performed every 2 wk in the first 2 mo. The risk of adverse reactions to antithyroid drugs is not negligible. The frequency of adverse reactions to MMI is dose-dependent (21, 62, 83–85). Because PTU and MMI may cross-react, adverse reactions

may occur even with a change in the drug regimen (53). Adverse drug reactions tend to occur at the beginning of treatment, but may also occur during maintenance therapy. Therefore, the patient must be monitored at prescribed intervals. Regarding monitoring, tests should include a complete blood count, differential white blood count, analyses of AST, ALT, γ -GTP, T-Bil, and creatine kinase (CK), and urinalysis.

2. Method for reducing antithyroid drug doses and maintenance therapy

Usually, thyroid function will stabilize 2–3 mo after starting treatment. Normalization of the FT3 level will occur after normalization of the FT4 level. Normalization of the TSH level will occur at a later time point. After the serum FT4 and FT3 levels are completely normalized, reduce the medication dose while monitoring the FT4 level. Once the TSH level becomes measurable, gradually reduce the antithyroid drug dose while maintaining the TSH level within the normal range (titration method). The usual maintenance dose of MMI ranges from 5 mg/every other day to 5 mg/d; the maintenance dose of PTU is 50 mg/d. Monitor the patient every 3–4 mo to confirm normal thyroid function. In the ATA guidelines, the maintenance dose of MMI is 5–10 mg/d and 100–150 mg/d for PTU. In the Brazilian guidelines, the maintenance dose of MMI is 5–10 mg/d and 50–100 mg/d for PTU. The maintenance dose for children should be approximately a quarter of the starting dose.

Although the usual maintenance dose of MMI ranges from approximately 5 mg/every other day to 10 mg/d, this may vary among individual patients. Testing to confirm normal thyroid function should be performed every 3–4 mo. Sometimes, treatment may be combined with LT4 to achieve functional stabilization of the thyroid gland.

If more than 6 mo have passed since treatment initiation and the thyroid function has not improved, or if a previously achieved therapeutic effect has weakened, consider drug

discontinuation. TSH-stimulation blocking antibodies may cause sudden elevations of TRAb and TSH levels.

3. Duration of treatment

Before starting treatment, it is important to explain to the patient how long he/she will need to take the drug and obtain their commitment to continued treatment. Generally, as children are not aware of their disease, they tend to exhibit poorer medication adherence. Specifically, they tend to stop taking the drug once the subjective symptoms disappear. A positive TRAb result can be used as an indicator of the duration of treatment (99). A previous report suggested that in children, the TRAb level does not decrease during the course of treatment to the same extent as in adults (72). Some cases will require an extended duration of treatment before a negative TRAb result is achieved. Patients with Graves' disease require long-term medication treatment. Accordingly, to support continued medication adherence, patients need to understand their illness and have a sense of participation in their treatment. Additionally, patients need social support.

There is no established method for accurately determining remission in Graves' disease; accordingly, there is no specific standard for treatment discontinuation. However, previous reports indicate that a longer duration of minimum dose treatment is associated with a higher remission rate (10, 71, 100, 101). Regarding the duration of antithyroid drug treatment, in "Endocrinology: Adult and Pediatric" by Jameson and De Groot (1), it is stated that children tend to exhibit poor medication compliance and require a longer treatment duration. If remission is not achieved after 3–4 yr of antithyroid drug treatment, another treatment method should be selected once the patient reaches 18–20 yr of age. In the ATA guidelines (19), the suggested duration of antithyroid drug treatment is 12–18 mo. The medication dose should be decreased or discontinued if the TSH level is normal. In such cases, the results of TRAb measurements can be

used to make such judgments. If remission cannot be achieved after 12–18 mo, either ^{131}I therapy or surgical treatment should be considered unless the patient wishes to continue antithyroid drug therapy (102, 103). In the Brazilian guidelines (44), the suggested duration of antithyroid drug therapy is 12–24 mo. In some studies, the remission rate did not improve after 18 mo of antithyroid drug therapy (43, 104). According to other studies, either ^{131}I therapy or surgical treatment should be considered if remission cannot be achieved after 2 yr of antithyroid drug therapy and if a child requires at least 2–4 yr to achieve remission (73, 105, 106).

Approximately 50% of children with Graves' disease in a multicenter prospective study in France achieved remission after 8–10 yr of long-term treatment with CBZ. This remission rate is higher than those in previous reports, but this rate did not improve after continued treatment beyond 10 yr (107). In the aforementioned study of Japanese children who developed Graves' disease at ages 15 yr or younger, the remission, non-remission, and therapy change rates of children who received treatment for more than 10 yr were 50, 43, and 8%, respectively with PTU, and 35, 45, and 20%, respectively with MMI (20). Given the retrospective nature of the study, the data from cases treated with PTU were relatively old. Thus, drug therapy was continued for longer periods of time. In contrast, data for MMI were obtained from recent cases, and switching to other treatment methods appeared to occur at an earlier stage. After taking these factors into consideration, the non-remission rates achieved with MMI and PTU appear to be almost the same. This suggests that the continuous use of MMI might have led to remission. In another study of 1,138 children (age ≤ 18 yr) with Graves' disease in Japan, the remission rate with antithyroid drug therapy was 46.2% after a median treatment period of 3.8 yr. As the remission rate usually improves for up to 5 yr after treatment initiation, this result suggests that the remission rate might be improved with

long-term antithyroid drug therapy (23). Based on the above results, nearly half of all patients might achieve remission regardless of the type of antithyroid drug, as long as the drug is used for a long period of time. Because drug therapy must be continued for more than 10 yr in some cases, it is not always necessary to suggest other treatment methods even if remission cannot be achieved within 1 or 2 yr.

In particular, drug therapy may be continued if the patient is a junior or high-school student and is preparing for an entrance examination in order to maintain stability in his/her school life, even if thyroid function has stabilized. Significant changes in a child's environment, such as starting a new school term or advancing to the next stage of schooling, may lead to recurrence if treatment is interrupted. Thus, the timing of treatment discontinuation requires careful consideration.

4. Lifestyle guidance for junior- or high-school students

For patients who are junior- or high-school students, it is important to provide guidance regarding school activities, including physical education (PE) classes and sporting activities. No clinical reports have discussed exercise guidance during treatment. However, patients should refrain from PE classes and sporting activities until thyroid function normalizes. After this normalization, no particular restrictions are needed except for participating in vigorous sporting activities. If normal thyroid function is maintained for an extended period of time, no restrictions are necessary, even for vigorous sporting activities.

In Japan, the traditional diet includes seaweed, and the intake of iodine from food is more common than in other countries. Because high amounts of iodide affect thyroid function, excess iodine intake has been reported to decrease the effects of antithyroid drugs in some countries with characteristically lower levels of iodine intake from food. However, in areas without iodine deficiency, iodine restrictions, during the initial

treatment of Graves' disease did not improve the treatment outcomes (108). In addition, iodine intake was not found to affect recurrence (109). Therefore, in Japan, it is not necessary to restrict dietary iodine intake as a component of Graves' disease management.

The JTA guidelines state that, "regardless of pre-treatment, during treatment, or during remission, patients with Graves' disease should not smoke". Smoking increases the risk of Graves' disease, reduces the effects of antithyroid drugs, and increases the recurrence rate. Many adolescents begin smoking as junior or senior high-school students and this coincides with the age of disease onset. Therefore, it is strongly recommended both adolescents with Graves' disease and their families refrain from smoking (8, 10).

6. Side Effects of Antithyroid Drugs

Recommendation

- 6-1. If minor adverse drug reactions (rash, mild hepatopathy, fever, arthralgia, myalgia, etc.) appear, continue treatment while monitoring; if symptoms do not improve, select a different drug. 2 (Consensus)
- 6-2. If serious adverse drug reactions (agranulocytosis, severe hepatopathy, MPO-ANCA-associated vasculitis syndrome, etc.) appear, discontinue drug treatment immediately. Subsequently, administer an inorganic iodine preparation to prevent deterioration of thyroid function. Switch the treatment to surgical treatment or, if necessary, radioiodine therapy. 1 (●○○)
- 6-3. A relationship between the use of MMI during the first trimester of pregnancy and MMI embryopathy (scalp defect, the umbilical cord hernia, remnant of ductus omphaloentericus, tracheoesophageal fistula, esophageal atresia, choanal atresia, etc.) in newborns has been suggested. Use of MMI should be avoided during the first trimester of pregnancy. 1 (●●○)

Explanation

The risk of adverse reactions to antithyroid drugs is certainly not negligible. The frequency of adverse reactions to MMI is known to be dose-dependent (60). Approximately 5–50% of MMI users experience minor adverse drug reactions such as rash or mild hepatic dysfunction (20, 23, 62); however, patients affected by these reactions tend to recover naturally. An antihistamine drug may be used concurrently in some cases. If the patient does not recover from these reactions, the other type of antithyroid drug should be used. Serious adverse drug reactions, including agranulocytosis, severe hepatopathy, polyarthritis, and MPO-ANCA-associated vasculitis syndrome occur in 0.1–1.0% of antithyroid drug users (59). If a patient develops such a severe reaction, the antithyroid drug should be discontinued immediately and the patient should be referred to a specialist. Because PTU and MMI exhibit cross-reactivity, adverse reactions may occur even if the drugs are switched (53). In such cases, an inorganic iodine preparation should be administered rather than the other type of antithyroid drug, and non-drug treatment options should be selected.

In a study of Japanese children who developed Graves' disease at age 15 yr or younger, the adverse reaction rates were 16.0% in the low MMI group, 29.2% in the high MMI group, 5.6% in the low PTU group, and 45.9% in the high PTU group; the difference between the low PTU and high PTU groups was significant (20).

In a study of Japanese children who developed Graves' disease at age 18 yr or younger, the frequencies of adverse drug reactions were 21.4% among all MMI users and 18.8% among all PTU users. Most patients developed adverse reactions within 3 mo of initiation of drug therapy, and PTU users more frequently experienced late-onset adverse reactions compared with MMI users (23).

MPO-ANCA-associated vasculitis syndrome is a serious adverse drug reaction that tends to occur at or beyond 1 yr of treatment (63–66). Among PTU users, the MPO-ANCA positive

rate is higher in children (64%). In a study that included adult patients, PTU users were approximately 40 times more susceptible to MPO-ANCA-associated vasculitis syndrome compared to MMI users. However, there was no association between vasculitis severity and MPO-ANCA antibody levels (59, 64). Approximately 20% of MPO-ANCA-positive patients develop vasculitis. Patients who use PTU for extended periods of time should undergo an annual serum MPO-ANCA measurement and urinalysis should be performed for those with positive results. During the course of treatment, if the patient has fever, rash, arthralgia, myalgia, or common cold symptoms, MPO-ANCA-associated vasculitis should be suspected and the serum MPO-ANCA level should be measured. Urinalysis is necessary to avoid missing the signs of hematuria due to nephritis. A change in the drug regimen should be considered for patients with high MPO-ANCA antibody levels. If the antibody level is low and the patient is asymptomatic, it should be explained that the MPO-ANCA test was positive and the patient is at risk of developing MPO-ANCA-associated vasculitis syndrome. After obtaining consent, PTU use can then be continued. High dose adrenal corticosteroid therapy, immunosuppressants, or hemodialysis should be used for MPO-ANCA-associated vasculitis syndrome, with the treatment choice depending on disease severity. The prognosis of PTU-induced MPO-ANCA-associated vasculitis is reported to be better than that of other primary ANCA-associated vasculitis syndromes (66).

Serious adverse drug reactions, such as agranulocytosis, severe hepatopathy, or polyarthritis, tend to appear within 3 mo after treatment initiation (59); however, these reactions may also occur several months later (110). If a patient develops such a reaction, discontinue use of the antithyroid drug immediately and switch to an inorganic iodine preparation including potassium iodide solution at 10–20 mg/d (QD) or 1–2 potassium iodide pills per day (inorganic iodine = 38.2 mg/pill). Treatment with

an inorganic iodine preparation may induce the development of escape phenomenon, which could exacerbate hyperthyroidism. In such cases, the patient should be referred immediately and at an early stage to a medical institution with specialists in surgical treatment or ^{131}I therapy.

Agranulocytosis, which is dependent on the antithyroid drug dose, reportedly occurs in 0.35% of cases (85, 111, 112). Based on aggregated data from a study of Japanese children with agranulocytosis, the dose of MMI at the time of onset was 20–45 mg/d and the treatment period ranged from 15 to 1,344 d. Patients developed agranulocytosis after receiving more than 20 mg/d of MMI, regardless of the treatment period (22). To treat agranulocytosis, granulocyte colony stimulating factor (G-CSF) should be administered according to the severity (113, 114).

A US study (115) reported that serious hepatopathy was more common in patients younger than 17 yr who were treated with PTU (23 of 76 patients with severe hepatopathy). In contrast, minor hepatopathy was more common in patients 61 yr or older who were treated with MMI (22 of 85 patients). Based on these results, use of PTU is not recommended for children in the US (11–18, 116). However, in Japan, aggregated data between 1995 and 2007 in patients aged 15 yr or younger who had serious hepatopathy failed to indicate PTU-induced liver failure in the “Study on Intractable Hepatobiliary Diseases” by the Health and Labour Sciences Research Grant. Based on information for adverse reactions submitted by two Japanese pharmaceutical companies that handle antithyroid drugs, no cases of PTU-induced liver failure have been reported since 1999 (117). However, according to the retrieved data, two Japanese children developed serious hepatitis and one died (118, 119). In comparison with the US, periodic hepatic function monitoring and earlier action may have led to a reduced number of patients with serious hepatitis (120). However, PTU should still be used for children with caution.

The use of MMI during the first trimester of

pregnancy has been suggested to be associated with MMI embryopathy (e.g., scalp defects, umbilical cord hernia, ductus omphaloentericus, tracheoesophageal fistula, esophageal atresia, and choanal atresia) in newborns (53, 68). All treatment guidelines suggest use of PTU, rather than MMI, during the first trimester of pregnancy.

7. Criteria for Antithyroid Drug Discontinuation

Recommendation

- 7-1. During continued drug therapy, if normal thyroid function is maintained with the maintenance dose of an antithyroid drug (approximately 5 mg of MMI/every other day to 5 mg/d), consider discontinuation of the drug. 2 (●○○)
- 7-2. If the goiter decreases in size and negative TRAb results are maintained, the patient may have achieved remission. 2 (●○○)
- 7-3. Continue using an antithyroid drug (1 tablet every other day) for more than 6 mo. If thyroid function is normalized, it may be possible to discontinue drug therapy. 2 (Consensus)
- 7-4. Drug therapy may be continued with consideration of the patient's school life (e.g., preparation for entrance examinations). 2 (Consensus)
- 7-5. Most recurrences occur within 1 yr of drug discontinuation. However, recurrences may also occur beyond 1 yr after discontinuation. Periodic check-up is required during remission. 1 (Consensus)

Explanation

There are no accurate predicting factors for the remission of Graves' disease; therefore, there is currently no specific standard for treatment discontinuation. Patients with a younger age, larger goiters, higher serum T3/T4 ratios, severity of pre-treatment hyperthyroidism, and persistent positive TRAb results have a greater risk of recurrence (75–78, 121–127). In children,

the reported remission rates vary (18–65%), but most studies suggest a rate of approximately 30% (29, 100, 122, 128–130). However, higher remission rates have been associated with longer minimum dose treatment durations (4.3 ± 1.5 yr) (131). In most cases, antithyroid drug therapy can be continued for an extended period if remission cannot be achieved after 18–24 mo of treatment. Once remission is achieved, therapy discontinuation can be considered if normal thyroid function, including the TSH level, is maintained for more than 6 mo with a treatment regimen involving one antithyroid drug tablet every other day (8, 10, 132).

A negative TRAb result suggests the possibility of remission (133–136). According to the JTA guidelines, patients with negative TRAb results tend to have a significantly higher remission rate than those with positive results. However, even with negative results, approximately 30% of patients experienced a recurrence. In addition, approximately 30% of patients with positive results achieved remission. Therefore, accurate prediction of prognosis is very difficult (10).

The T3 suppression test was previously used to indicate the timing of antithyroid drug discontinuation (99). T3 (Thyronamin Tablet® 5 µg, 25 µg) at 1.5 µg/kg/d (75 µg/d maximum) TID should be administered for 7 days while continuing antithyroid drug therapy. If using the thyroid radioactive iodine uptake (RAIU) as an indicator, the RAIU (24-h value) should be measured after administering T3. If the RAIU is 30% or lower, the T3 suppression test result is considered to be positive. If using the serum T4 level as an indicator, T4 levels should be measured before and after administration of T3. Next, the rate of decrease from before to after T3 administration is calculated; if the serum T4 level has decreased by more than 30%, the T3 suppression test result is considered to be positive. According to a study of pediatric Graves' disease patients who were treated with PTU for more than 2 yr, the recurrence rate after

treatment discontinuation was 22.2% when the T3 suppression test was used as an indicator. In another study in adult patients with Graves' disease who were treated with MMI for more than 2 yr, a T3 suppression test was performed and treatment was discontinued once 6 mo or more had passed since the normalization in TRAb levels. This study reported a recurrence rate of 22.0% (136). More recently, the T3 suppression test has been used less frequently to determine the timing of drug therapy discontinuation (7).

8. Surgical Treatment for Graves' Disease

Recommendation

- 8-1. Thyroidectomy is an effective treatment for Graves' disease. 2 (●●●)
- 8-2. The following are surgical indications: 1) the patient's condition is complicated by a thyroid cancer, 2) because of an adverse reaction, the patient cannot use any antithyroid drugs and does not wish to receive ¹³¹I therapy, 3) the patient has a large goiter and has not achieved remission with antithyroid drug treatment, 4) the patient's antithyroid drug compliance is poor, and the thyroid function is not stable, and 5) the patient wishes to achieve complete remission and regain his/her social life more quickly. 1 (Consensus)
- 8-3. Surgery must be performed by a skillful thyroid surgeon. 1 (●●○)
- 8-4. Total or near total thyroidectomy should be performed to reduce the remaining thyroid tissue as much as possible. 1 (●●○)
- 8-5. Children tend to have a higher recurrence rate and higher frequency of complications. 1 (●○)
- 8-6. The patient requires life-long thyroid hormone replacement therapy because of decreased thyroid gland function after thyroidectomy. 1 (●●○)

Explanation

1. Indications

Surgical treatment is effective for Graves'

disease. It is a quick and reliable method; however, the necessity of hospitalization, surgical scarring, and post-operative complications preclude its selection as a primary treatment option (8, 10). This method is used to treat patients who are not responsive to drug therapy, cannot continue drug therapy because of adverse reactions, cannot achieve remission after long-term drug therapy, wish to achieve remission more quickly, are complicated by thyroid cancer, have a large goiter, and/or exhibit poor medication adherence (8, 10). This treatment is indicated for children of age 5 yr or younger who require complete remission. Most patients who select surgery tend to do so for personal reasons such as poor medication adherence.

2. Complications

Hemorrhage, hoarseness due to recurrent laryngeal nerve paralysis, and hypoparathyroidism are known complications of surgery. A larger goiter is associated with an increased amount of bleeding during surgery, and the risks of blood transfusion are increased in children. Because the recurrent laryngeal nerves are thinner in children than in adults, pediatric cases must be handled with caution. Post-operative hypoparathyroidism might be prolonged in children as a result of growth-related bone metabolism.

According to a Japanese study that compared the surgical outcomes of 3 age groups—(1) 15 yr or younger (74 patients), (2) 16–20 yr (345 patients), and (3) 21 yr or older (1,478 patients)—, the respective recurrence rates at 5 yr after surgery in patients with less than 4 g of remaining thyroid tissue were 18, 10, and 8%, respectively. In Group (1), both recurrences and complications such as voice hoarseness occurred more frequently (137).

When surgery was performed by skillful thyroid surgeons, the incidence rates of permanent hypoparathyroidism and permanent recurrent laryngeal nerve paralysis were less than 2% and less than 1%, respectively (138–141).

3. Operative procedures

Hyperthyroidism should be well controlled before surgery by MMI, an inorganic iodine preparation, or a β -blocker. Dexamethasone is also useful to improve uncontrolled hyperthyroidism rapidly.

Children with Graves' disease exhibit high disease activity and have a higher recurrence rate. Therefore, total or near total thyroidectomy (i.e., < 3 g of remaining thyroid tissue) is recommended to reduce the remaining thyroid tissue as much as possible (142–144). In such cases, thyroid function will certainly decrease and thyroid hormone replacement therapy will be required (145, 146). According to the ATA guidelines (19), total or near total thyroidectomy is suggested for children younger than 5 yr, if a complete cure for hyperthyroidism is desired, or if the goiter is large (> 80 g). Other guidelines and reviews also suggest total or near total thyroidectomy in consideration of the risks of recurrence or bleeding during surgery.

The surgery must be performed by a skillful thyroid surgeon (147, 148).

9. ^{131}I Therapy for Graves' Disease

Recommendation

- 9-1. ^{131}I therapy is a reliable, effective, and safe treatment for Graves' disease. 2 (●●○)
- 9-2. ^{131}I therapy should be performed thoughtfully in children 18 yr or younger. In addition, ^{131}I therapy is generally contraindicated in children 5 yr or younger. 1 (●○○)
- 9-3. A specialist with sufficient experience should perform the procedure. 1 (●○○)
- 9-4. Before performing ^{131}I therapy, provide a sufficient explanation of the treatment and obtain consent from the patient. 1 (Consensus)
- 9-5. Prior to ^{131}I therapy, use an antithyroid drug or β -blocker to normalize thyroid function. 1 (●○○)
- 9-6. To reduce thyroid function with a single ^{131}I therapeutic procedure, a sufficient dose of

^{131}I should be given. 1 (●○○)

9-7. After ^{131}I therapy, thyrotoxicosis may be temporally exacerbated. 2 (●○○)

9-8. Patients who receive ^{131}I therapy are likely to develop hypothyroidism in the future. 1 (●○○)

Explanation

1. Indications

^{131}I therapy is a reliable, effective, and safe treatment for Graves' disease (149, 150). ^{131}I therapy had been generally contraindicated in patients 18 yr or younger. However, according to the "Guidelines for the Treatment of Graves' Disease in Japan, 2011", ^{131}I therapy can be performed with caution. This change was made to provide physicians with more options in cases that cannot tolerate other treatments (10). ^{131}I therapy should even be considered in children who do not respond at all to drug therapy, cannot receive drug therapy because of an adverse reaction, and/or refuse to have surgical treatment. The usefulness of ^{131}I therapy for pediatric patients has also been reported in several articles published overseas (151–154).

The absolute indications for ^{131}I therapy are patients who experienced serious adverse drug reactions during antithyroid drug therapy and do not wish to receive surgical treatment and patients who cannot use either of the antithyroid drugs and do not wish to receive surgical treatment (10). The relative indications are as follows: 1) patients who do not wish to use another treatment method, 2) those who can not achieve remission with an antithyroid drug and do not wish to continue drug therapy, 3) those with recurrent Graves' disease after surgery, 4) those who wish to receive a complete cure for hyperthyroidism, 5) those who wish to decrease the size of their goiter, and 6) those with a chronic disease, such as heart disease or diabetes mellitus, that lead to difficulties achieving control with drug therapy. The relative contraindication for ^{131}I therapy is the presence of severe thyroid-associated ophthalmopathy.

As a general rule, it should be ensured that the patient: 1) does not have complicating thyroid cancer, 2) is not pregnant or lactating and is not likely to become pregnant in the next 6 mo, 3) is 19 yr or older, and 4) does not have thyroid-associated ophthalmopathy.

¹³¹I therapy can only be used in children if other treatment options are not possible. In such cases, the physician must fully explain the therapy, consult with the patient and their family, and decide whether to select this treatment method (155).

2. Practical guidelines

Restrict iodine intake more than 1 week prior to ¹³¹I therapy, and discontinue the antithyroid drug more than 3 days prior to ¹³¹I therapy. Measure the RAIU (156) to confirm that iodine is restricted. Methods have not yet been established to determine the dose of ¹³¹I required to normalize the thyroid function after this treatment.

The ATA guidelines (19) state that ¹³¹I therapy should be avoided in children younger than 5 yr of age. ¹³¹I therapy is acceptable in children aged 5–10 yr if less than 10 mCi of ¹³¹I is administered. In patients 10 yr or older, ¹³¹I therapy is acceptable if the dose exceeds 150 μ Ci/g of thyroid tissue (157–160).

The Brazilian guidelines state that ¹³¹I therapy is acceptable in patients 10 yr or older if the dose exceeds 160 μ Ci/g of thyroid tissue. For patients with a smaller goiter, ¹³¹I therapy is useful at a ¹³¹I dose between 10 and 15 mCi. ¹³¹I dose exceeding 150 μ Ci/g of thyroid tissue induced hypothyroidism in 95% of patients (73, 161, 162).

Kaguelidou suggested that the ¹³¹I dose should be between 220 and 275 μ Ci/g of thyroid tissue (74).

Rivkees recommended ¹³¹I should be administered at a fixed activity dose of 15 mCi. If calculating the dose according to thyroid weight, the activity should exceed 150 μ Ci/g of thyroid tissue. If the thyroid weight is between 30 and 80 g (163), the ¹³¹I dose should be as high as 200

to 300 μ Ci/g of thyroid tissue (106, 164).

After ¹³¹I therapy, thyrotoxicosis may be temporarily exacerbated. If necessary, use an antithyroid drug, inorganic iodine preparation, or corticosteroids (165, 166).

The TRAb level will be elevated in the 6-mo period after ¹³¹I therapy, which might significantly affect the state of hyperthyroidism (167). Thyroid function should be evaluated periodically and, if necessary, an antithyroid drug should be used. After ¹³¹I therapy, note that the patient may develop or experience exacerbated thyroid-associated ophthalmopathy.

The second ¹³¹I therapy should be considered for early achievement of normo- or hypo-thyroid function if antithyroid drug therapy cannot be discontinued after 1 yr.

After ¹³¹I therapy, it is difficult to maintain normal thyroid function for a long period, and hypothyroidism will eventually develop. Thyroid hormone replacement therapy will be required in most patients (168, 169).

3. Malignant tumors and teratogenic and genetic disorders

The relative risk of developing thyroid cancer following external irradiation of the head and neck was evaluated in children aged 5 yr or younger, 5–10 yr, and 10–15 yr; the calculated risks were 9.0, 5.4, and 1.8, respectively (149). However, overseas studies of ¹³¹I therapy showed no increase in the risk of malignant diseases, including thyroid cancer (151–154, 160, 170–180).

Excluding children younger than 10 yr who were administered more than 10 mCi of ¹³¹I and children 5 yr or younger, there is no evidence to suggest that ¹³¹I therapy increases the risk of malignant tumors, including thyroid cancer, or risk of teratogenic or genetic disorders (19, 73, 74, 106, 181).

According to a nation-wide study in the UK, the number of children and adolescents aged 20 yr or younger, treated with ¹³¹I therapy, is increasing slightly. This increase has been attributed to the decreased hesitation surrounding the use of ¹³¹I

therapy, as well as the lowered indication age (from 18 to 11 yr) (182).

Japan is the only nation to suffer atomic bombings. In addition, Japan recently experienced an accident at the Tokyo Electric Power Company Fukushima Daiichi Nuclear Power Station after the Great East Japan Earthquake. Therefore, Japanese citizens are very sensitive about “radiation”. If ^{131}I therapy must be used, it is important that a detailed explanation is provided by physicians, and that consent is obtained from patients. Subsequently, therapy should be performed by experienced specialists (183–185).

10. Thyroid Storm

Recommendation

- 10-1. Thyroid storm is a severe, life-threatening form of thyrotoxicosis. 1 (Consensus)
- 10-2. A patient with thyroid storm must be treated in an intensive care unit under whole-body management. The patient must promptly receive a large fluid infusion, body temperature management, large dose of an antithyroid drug, inorganic iodine preparation, β -blocker, and adrenal corticosteroid. If the patient's clinical symptoms do not improve, plasmapheresis should be performed. 1 (Consensus)

Explanation

1. Definition, epidemiology, and diagnosis

Thyroid storm is an acute exacerbation of thyrotoxicosis. Thyrotoxicosis is caused by an untreated or poorly controlled underlying thyroid condition; when accompanied by a strong stressor, such as infection, trauma, or surgery, multiple organ dysfunction will occur consequent to a disturbance in the mechanism that compensates for excessive thyroid hormone action. This life-threatening clinical condition requires emergency treatment (186). Infection is the most common trigger of thyroid storm. In addition, a patient may develop thyroid storm

after an emergency operation if the presence of Graves' disease is overlooked. The reported frequency of thyroid storm among patients with thyrotoxicosis is 1.0% (187); additionally, 1–2% of patients with thyrotoxicosis require hospitalization, and the fatality rate associated with this condition is 10–75% (188). A taskforce committee of the JTA and the Japan Endocrine Society for the “Establishment of Diagnostic Criteria and Nationwide Surveys for Thyroid Storm” conducted an epidemiological study in Japan in 2009, in which the estimated number of patients with thyroid storm was approximately 150 per year, or 0.22% of all thyrotoxicosis patients. Thyroid storm is an extremely rare clinical condition with a fatality rate of 11.0% (186). The pathogenic mechanisms underlying thyroid storm are unknown, and the associated fatality rate is high (186–188). This disease requires emergency treatment.

Regarding thyroid storm in children, a previous study reported that this disease occurs in 0.1–3 per 100,000 children (189); however, there are not enough epidemiological data (187). In Japan, according to the retrieved data, only around 10 pediatric cases have been reported; however, the actual situation regarding thyroid storm remains unknown. Although most children undergo physical check-ups at school and visit pediatric clinics because of common colds, Graves' disease may be overlooked in this population. Many of these children develop thyroid storm and finally receive treatment at emergency medical facilities. Thyroid diseases are rarely included in a differential diagnosis, particularly in pediatric emergency medical facilities. Many children who see physicians for central nervous system manifestations accompanied by fever are diagnosed with acute encephalopathy; thyroid storm may be overlooked (190).

The Thyroid Storm Scoring System can be used to diagnose thyroid storm according to symptoms and signs (191). The JTA also established and published diagnostic criteria for thyroid storm (186) (Table 4). A diagnosis

Table 4. Criteria for the diagnosis of thyroid storm (2nd Edition) (Japan Thyroid Association)

[Definite Case]

- a. Thyrotoxicosis and at least one central nervous system (CNS) manifestation and one of the following: fever, tachycardia, congestive heart failure (CHF), or gastrointestinal (GI)/hepatic manifestations.
- b. Thyrotoxicosis and at least three of fever, tachycardia, CHF, or GI/hepatic manifestations.

[Suspected case]

- a. Thyrotoxicosis and a combination of two of the following: fever or tachycardia or CHF or GI/hepatic manifestations.
- b. Patients who meet the diagnostic criteria for "Definite Case" except that serum FT3 or FT4 values are not available, but in whom data before or after the episode suggest that they are thyrotoxic at the time of thyroid storm.

Definitions

Thyrotoxicosis: Elevated FT3 or FT4.

CNS manifestations: Restlessness, delirium, mental aberration/psychosis, somnolence/lethargy, convulsion, coma including a score of 1 or higher on the Japan Coma Scale (JCS), or 14 or lower on the Glasgow Coma Scale (GCS).

Fever: 38 degrees Celsius or higher.

Tachycardia: 130 beats/min or higher (arrhythmias such as atrial fibrillation are evaluated by measuring the heart rate).

CHF: The patient presents with severe symptoms such as pulmonary edema, moist rales for more than half the lung field, or cardiogenic shock. The patient's CHF is categorized as Class IV by the New York Heart Association classification or Class III or higher by the Killip classification.

GI/hepatic manifestations: The patient presents with nausea, vomiting, diarrhea, or a bilirubin of > 3 mg/dL.

Exclusions and Provisos

Cases are excluded if other underlying diseases are clearly causing any of the following symptoms: fever (e.g., pneumonia and malignant hyperthermia), impaired consciousness (e.g., psychiatric disorders and cerebrovascular disorders), heart failure (e.g., acute myocardial infarction), and liver disorders (e.g., viral hepatitis and acute liver failure). However, some of these disorders trigger thyroid storm. Therefore, it is difficult to determine whether the symptom is caused by thyroid storm or is simply a symptom of an underlying disease that is possibly triggered by thyroid storm; therefore, the symptom should be regarded as being due to a thyroid storm that is caused by these precipitating factors. Clinical judgment in this matter is required.

must be made based on these clinical symptoms and signs (189).

2. Treatment

A patient with thyroid storm must be treated in an intensive care unit. In addition to respiratory support, resuscitation, and whole-body monitoring, the following treatment approach should be promptly undertaken: a large initial fluid infusion (10–20 mL/kg/h), cooling blankets, body temperature management with antipyretics (acetaminophen at 10 mg/kg/dose, maximum of 500 mg TID to QID), a large dose of an antithyroid drug (PTU at 15–30 mg/kg/d,

adult dose of 800–1,200 mg/d TID to QID; MMI at 1.0–2.0 mg/kg/d, adult dose of 60–80 mg/d TID to QID), inorganic iodine preparation (125–250 mg/d TID to QID, 3–6 potassium iodide pills 1 h after administration of the antithyroid drug), β -blocker (initial intravenous administration of propranolol at 10 μ g/kg), and adrenal corticosteroids (dexamethasone at 0.6 mg/kg/d; hydrocortisone at 15 mg/kg/d, TID) (19, 186–188). An antibacterial drug should be administered concurrently if thyroid storm has been triggered by an infection. If clinical symptoms do not improve, plasmapheresis should be performed. PTU, adrenal corticosteroids, inorganic iodine

preparations, and β -blockers suppress the T4 to T3 conversion. Usually, PTU is considered more effective than MMI for thyroid storm; however, there is no clear evidence to support this view. Inorganic iodine preparations must be used 1 h after administration of the antithyroid drug.

Conflict of Interest for Committee Members:

Each committee member was asked to report potential conflicts of interest that arose during the preparation of these guidelines. We have no conflicts of interest to declare. In accordance with the rules of the Japanese Society for Pediatric Endocrinology, the Conflict of Interest Standards presented by the Japan Pediatric Society must be observed.

Acknowledgments

Funds for development of these guidelines were provided by the Japanese Society for Pediatric Endocrinology.

We are very grateful to the following members of the Committee on Pharmaceutical Affairs, Japanese Society for Pediatric Endocrinology, and the Pediatric Thyroid Disease Committee, Japan Thyroid Association for their collaboration on this project: Toru Kikuchi, Tomohiro Kamoda, Saori Kinjyo, Jyunji Takaya, Hidenori Haruna, Ichiro Miyata, Naoko Arata, Fumito Akasu, Hiroaki Inomata, Kazumichi Onigata, Shigetaka Sugihara, Keisuke Nagasaki, Satoshi Narumi, Soroku Nishiyama, Yukihiro Hasegawa, Shuji Fukata, Mako Fujiwara, Takashi Misaki, Tetsuya Mizokami, Naoko Momotani, Susumu Yokoya, and Hiroshi Yoshimura.

Appendix

1. Preparation Funds

The preparation of these guidelines was funded by the Japanese Society for Pediatric Endocrinology and the Japan Thyroid Association.

2. Preparation Process

2-1. Understanding the current situation

On April 27, 2013, at the 14th Committee Meeting

of Pediatric Thyroid Diseases of the Japan Thyroid Association, a revision of the guidelines was suggested. On November 16, 2013, at the 15th Committee Meeting of Pediatric Thyroid Diseases, opinions were sought regarding clinical questions on the current guidelines. On December 14, 2013, a preparation committee meeting was held to draft these clinical questions. On April 26, 2014 and November 15, 2014, at the 16th and 17th Committee Meetings for Pediatric Thyroid Diseases, respectively, opinions were sought on a draft modification of the guidelines.

2-2. External evaluation

From January 1 to January 31, 2016, a draft of the Guideline was posted on the website to allow members of the Japanese Society for Pediatric Endocrinology, as well as the Japan Thyroid Association, to view the draft and to solicit their opinions.

Based on these opinions, a draft of the revision was created on March 10, 2016.

The prepared draft was reviewed by members of the Guidelines Committee of the Japanese Society for Pediatric Endocrinology (including external members) to evaluate its scientific integrity as medical guidelines, as well as the appropriateness of the contents. In response to suggestions from the Guideline Committee Members (dated on March 22, 2016), the draft was again modified. Prior to its release, the final version of the Guideline was approved on April 6, 2016 by the Executive Board Members of the Japanese Society for Pediatric Endocrinology, and on April 22, 2016 by the Executive Board Members of the Japan Thyroid Association.

2-3. Coordination with other related academic societies

Information on preparation-related tasks, progress, and an understanding of the guidelines was shared via close communication maintained with the Japan Thyroid Association during preparation committee meetings.

3. Revision Schedule

These guidelines are scheduled to be revised within 5 years of their release. Preparation committee members who will engage in this revision will be appointed by the Executive Board Members of the Japanese Society for Pediatric Endocrinology, as well as the Japan Thyroid Association. In the occurrence of any situations that might have a significant impact on the contents of the guidelines, or if either the Executive Board Members of the Japanese Society for Pediatric Endocrinology or the Japan Thyroid Association consider that urgent changes are required, modifications to the guidelines can be made as "recommendations."

References

1. Marino M, Vitti P, Chiovato L. Graves' disease. In: Jameson Jr, De Groot LJ, editors. *Endocrinology: adult and pediatric*, 7th Ed. Philadelphia, PA: Saunders and Elsevier; 2016. p. 1437-64.
2. LaFranchi SH, Hanna CE. Hyperthyroidism in the neonatal period and childhood. In: Braverman LE, Cooper DS, editors. *Werner and Ingbar's The thyroid: A Fundamental and Clinical Text*, 10th Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. p. 803-14.
3. Japan Thyroid Association. Guidelines for the Treatment of Graves' Disease with Antithyroid Drug in Japan, 2006. Tokyo: Nankodo Co., Ltd.; 2006 (in Japanese).
4. Huang SA, LaFranchi SH. Graves' disease. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE, editors. *Nelson textbook of pediatrics*. 20th ed. Philadelphia: Elsevier, Inc.; 2016. p. 2681-4.
5. Fisher DA. Hyperthyroidism. In: Rudolph CD, Rudolph AM, Lister GE, First LR, Gershon AA, editors. *Rudolph's Pediatrics*. 22nd ed. New York: McGraw-Hill Companies Inc.; 2011. p. 2039-40.
6. Japan Thyroid Association. Guidelines for the Diagnosis of Graves, 2013. <http://www.japanthyroid.jp/doctor/guideline/japanese.html>.
7. Sato H, Harada S, Yokoya S, Tanaka T, Asayama K, Mori M, *et al*. Treatment for childhood-onset Graves disease in Japan: results of a nationwide questionnaire survey of pediatric endocrinologists and thyroidologists. *Thyroid* 2007;17: 67–72. [Medline] [CrossRef]
8. Sato H, Sasaki N, Harada S, Tanaka T, Akasu F, Asayama K, *et al*. Guidelines for the Treatment of Childhood-Onset Graves' Disease with Antithyroid Drug in Japan, 2008. *J Jpn Pediatr Soc* 2008;112: 946–52 (in Japanese).
9. Japan Thyroid Association. *Handbook of Radioiodine (¹³¹I) Therapy for Graves' Disease in Japan*, 2007. Kyoto; 2007 (in Japanese).
10. Japan Thyroid Association. *Guidelines for the Treatment of Graves' Disease in Japan*, 2011. Tokyo: Nankodo Co., Ltd.; 2011 (in Japanese).
11. Ruiz JK, Rossi GV, Vallejos HA, Brenet RW, Lopez IB, Escribano AA. Fulminant hepatic failure associated with propylthiouracil. *Ann Pharmacother* 2003;37: 224–8. [Medline] [CrossRef]
12. Bahn RS, Burch HS, Cooper DS, Garber JR, Greenlee CM, Klein IL, *et al*. The role of propylthiouracil in the management of Graves disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid* 2009;19: 673–4. [Medline] [CrossRef]
13. FDA. U.S. Food and Drug Administration information for healthcare professionals-propylthiouracil-induced liver failure. 2009. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm162701.htm.
14. Up To Date patient information. antithyroid drugs. www.uptodate.com/patients/content/topic.do?topicKey=~K7dgOAlby0pAB7&source=see_link.
15. Eunice Kennedy Shriver National Institute of Child Health and Human Development 2008 Conference Proceeding. Hepatic Toxicity Following Treatment for Pediatric Graves' Disease Meeting: October 28, 2008. <http://bpca.nichd.nih.gov/outreach/index.cfm>.
16. Rivkees SA, Mattison DR. Propylthiouracil (PTU) hepatotoxicity in children and recommendations for discontinuation of use. *Int J Pediatr Endocrinol* 2009; 132041. [Medline] [CrossRef]
17. Cooper DS, Rivkees SA. Putting propylthiouracil in perspective. *J Clin Endocrinol Metab* 2009;94: 1881–2. [Medline] [CrossRef]
18. Rivkees SA, Mattison DR. Ending propylthiouracil-induced liver failure in children. *N Engl J Med* 2009;360: 1574–5. [Medline] [CrossRef]
19. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, *et al*. American Thyroid Association American Association of Clinical Endocrinologists. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid* 2011;21: 593–646. [Medline] [CrossRef]

20. Sato H, Minagawa M, Sasaki N, Sugihara S, Kazukawa I, Minamitani K, *et al.* Comparison of methimazole and propylthiouracil in the management of children and adolescents with Graves disease: efficacy and adverse reactions during initial treatment and long-term outcome. *J Pediatr Endocrinol Metab* 2011;24: 257–63. [[Medline](#)] [[CrossRef](#)]
21. Sato H, Sasaki N, Minamitani K, Minagawa M, Kazukawa I, Sugihara S, *et al.* Higher dose of methimazole causes frequent adverse effects in the management of Graves disease in children and adolescents. *J Pediatr Endocrinol Metab* 2012;25: 863–7. [[Medline](#)] [[CrossRef](#)]
22. Minamitani K, Oikawa J, Wataki K, Kashima K, Hoshi M, Inomata H, *et al.* A report of three girls with antithyroid drug-induced agranulocytosis; Retrospective analysis of 18 cases aged 15 years or younger reported between 1995 and 2009. *Clin Pediatr Endocrinol* 2011;20: 39–46. [[Medline](#)] [[CrossRef](#)]
23. Ohye H, Minagawa A, Noh JY, Mukasa K, Kunii Y, Watanabe N, *et al.* Antithyroid drug treatment for graves disease in children: a long-term retrospective study at a single institution. *Thyroid* 2014;24: 200–7. [[Medline](#)] [[CrossRef](#)]
24. Sato H, Minamitani K, Minagawa M, Kazukawa I, Sugihara S, Wataki K, *et al.* Clinical features at diagnosis and responses to antithyroid drugs in younger children with Graves disease compared with adolescent patients. *J Pediatr Endocrinol Metab* 2014;27: 677–83. [[Medline](#)] [[CrossRef](#)]
25. Burch HB. Overview of the clinical manifestations of thyrotoxicosis. In: Braverman LE, Cooper DS, editors. *Werner and Ingbar's The thyroid: A Fundamental and Clinical Text*, 10th Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. p. 434-40.
26. Nandi-Munshi D, Taplin CE. Thyroid-related neurological disorders and complications in children. *Pediatr Neurol* 2015;52: 373–82. [[Medline](#)] [[CrossRef](#)]
27. Cassio A, Corrias A, Gualandi S, Tato L, Cesaretti G, Volta C, *et al.* Influence of gender and pubertal stage at diagnosis on growth outcome in childhood thyrotoxicosis: results of a collaborative study. *Clin Endocrinol (Oxf)* 2006;64: 53–7. [[Medline](#)] [[CrossRef](#)]
28. Takamatsu J, Kobe N, Ito M, Ohsawa N. Body height and weight of patients with childhood onset and adult onset thyrotoxicosis. *Endocr J* 1999;46(Suppl): S101–3. [[Medline](#)] [[CrossRef](#)]
29. Lazar L, Kalter-Leibovici O, Pertzalan A, Weintrob N, Josefsberg Z, Phillip M. Thyrotoxicosis in prepubertal children compared with pubertal and postpubertal patients. *J Clin Endocrinol Metab* 2000;85: 3678–82. [[Medline](#)] [[CrossRef](#)]
30. Krassas GE, Segni M, Wiersinga WM. Childhood Graves ophthalmopathy: results of a European questionnaire study. *Eur J Endocrinol* 2005;153: 515–21. [[Medline](#)] [[CrossRef](#)]
31. Gogakos AI, Boboridis K, Krassas GE. Pediatric aspects in Graves orbitopathy. *Pediatr Endocrinol Rev* 2010;7(Suppl 2): 234–44. [[Medline](#)]
32. Villanueva R, Greenberg DA, Davies TF, Tomer Y. Sibling recurrence risk in autoimmune thyroid disease. *Thyroid* 2003;13: 761–4. [[Medline](#)] [[CrossRef](#)]
33. Brix TH, Kyvik KO, Christensen K, Hegedüs L. Evidence for a major role of heredity in Graves disease: a population-based study of two Danish twin cohorts. *J Clin Endocrinol Metab* 2001;86: 930–4. [[Medline](#)]
34. Simmonds MJ. GWAS in autoimmune thyroid disease: redefining our understanding of pathogenesis. *Nat Rev Endocrinol* 2013;9: 277–87. [[Medline](#)] [[CrossRef](#)]
35. Ban Y. Genetic factors of autoimmune thyroid diseases in Japanese. *Autoimmune Dis.* 2012;2012:236981. doi: [10.1155/2012/236981](https://doi.org/10.1155/2012/236981). Epub 2011 Dec 27.
36. Davies TF, Latif R, Yin X. New genetic insights from autoimmune thyroid disease. *J Thyroid Res* 2012;623852. [[Medline](#)] [[CrossRef](#)]
37. Iwama S, Ikezaki A, Kikuoka N, Kim HS, Matsuoka H, Yanagawa T, *et al.* Association of HLA-DR, -DQ genotype and CTLA-4 gene polymorphism with Graves disease in Japanese children. *Horm Res* 2005;63: 55–60. [[Medline](#)]
38. Brent GA. Environmental exposures and autoimmune thyroid disease. *Thyroid* 2010;20: 755–61. [[Medline](#)] [[CrossRef](#)]
39. Iwaku K, Noh JY, Minagawa A, Kosuga Y, Suzuki M, Sekiya K, *et al.* Determination of pediatric reference levels of FT3, FT4 and TSH

- measured with ECLusys kits. *Endocr J* 2013;60: 799–804. [[Medline](#)] [[CrossRef](#)]
40. Uchida T, Takeno K, Goto M, Kanno R, Kubo S, Takahashi S, *et al.* Superior thyroid artery mean peak systolic velocity for the diagnosis of thyrotoxicosis in Japanese patients. *Endocr J* 2010;57: 439–43. [[Medline](#)] [[CrossRef](#)]
 41. Kamijo K. Study on cutoff value setting for differential diagnosis between Graves disease and painless thyroiditis using the TRAb (Elecys TRAb) measurement via the fully automated electrochemiluminescence immunoassay system. *Endocr J* 2010;57: 895–902. [[Medline](#)] [[CrossRef](#)]
 42. Shishiba Y, Kamijyo K, Kurihara H, Sasaki J, Ishikawa N, Ozawa Y, *et al.* Differential diagnosis of silent thyroiditis from Graves' disease in thyrotoxicosis by the measurement of the urinary iodine. *Clin Endocrinol (Tokyo)* 2002;50: 629–40 (in Japanese).
 43. Franklyn JA, Boelaert K. Thyrotoxicosis. *Lancet* 2012;379: 1155–66. [[Medline](#)] [[CrossRef](#)]
 44. Smith J, Brown RS. Persistence of thyrotropin (TSH) receptor antibodies in children and adolescents with Graves disease treated using antithyroid medication. *Thyroid* 2007;17: 1103–7. [[Medline](#)] [[CrossRef](#)]
 45. Nagasaki T, Inaba M, Kumeda Y, Fujiwara-Ueda M, Hiura Y, Nishizawa Y. Significance of thyroid blood flow as a predictor of methimazole sensitivity in untreated hyperthyroid patients with Graves disease. *Biomed Pharmacother* 2007;61: 472–6. [[Medline](#)] [[CrossRef](#)]
 46. Cooper DS. Antithyroid drugs in the management of patients with Graves disease: an evidence-based approach to therapeutic controversies. *J Clin Endocrinol Metab* 2003;88: 3474–81. [[Medline](#)] [[CrossRef](#)]
 47. Muldoon BT, Mai VQ, Burch HB. Management of Graves disease: an overview and comparison of clinical practice guidelines with actual practice trends. *Endocrinol Metab Clin North Am* 2014;43: 495–516. [[Medline](#)] [[CrossRef](#)]
 48. Burch HB, Burman KD, Cooper DSA. A 2011 survey of clinical practice patterns in the management of Graves disease. *J Clin Endocrinol Metab* 2012;97: 4549–58. [[Medline](#)] [[CrossRef](#)]
 49. Wartofsky L, Glinioer D, Solomon B, Nagataki S, Lagasse R, Nagayama Y, *et al.* Differences and similarities in the diagnosis and treatment of Graves disease in Europe, Japan, and the United States. *Thyroid* 1991;1: 129–35. [[Medline](#)] [[CrossRef](#)]
 50. Perrild H, Grütters-Kieslich A, Feldt-Rasmussen U, Grant D, Martino E, Kayser L, *et al.* Diagnosis and treatment of thyrotoxicosis in childhood. A European questionnaire study. *Eur J Endocrinol* 1994;131: 467–73. [[Medline](#)] [[CrossRef](#)]
 51. Lee HS, Hwang JS. The treatment of Graves disease in children and adolescents. *Ann Pediatr Endocrinol Metab* 2014;19: 122–6. [[Medline](#)] [[CrossRef](#)]
 52. Léger J, Kaguelidou F, Alberti C, Carel JC. Graves disease in children. *Best Pract Res Clin Endocrinol Metab* 2014;28: 233–43. [[Medline](#)] [[CrossRef](#)]
 53. Cooper DS. Antithyroid drugs. *N Engl J Med* 2005;352: 905–17. [[Medline](#)] [[CrossRef](#)]
 54. Saberi M, Sterling FH, Utiger RD. Reduction in extrathyroidal triiodothyronine production by propylthiouracil in man. *J Clin Invest* 1975;55: 218–23. [[Medline](#)] [[CrossRef](#)]
 55. Stanley MM, Astwood EB. 1-Methyl-2-mercaptoimidazole; an antithyroid compound highly active in man. *Endocrinology* 1949;44: 588–9. [[Medline](#)] [[CrossRef](#)]
 56. Nicholas WC, Fischer RG, Stevenson RA, Bass JD. Single daily dose of methimazole compared to every 8 hours propylthiouracil in the treatment of hyperthyroidism. *South Med J* 1995;88: 973–6. [[Medline](#)] [[CrossRef](#)]
 57. He CT, Hsieh AT, Pei D, Hung YJ, Wu LY, Yang TC, *et al.* Comparison of single daily dose of methimazole and propylthiouracil in the treatment of Graves hyperthyroidism. *Clin Endocrinol (Oxf)* 2004;60: 676–81. [[Medline](#)] [[CrossRef](#)]
 58. Emiliano AB, Governale L, Parks M, Cooper DS. Shifts in propylthiouracil and methimazole prescribing practices: antithyroid drug use in the United States from 1991 to 2008. *J Clin Endocrinol Metab* 2010;95: 2227–33. [[Medline](#)] [[CrossRef](#)]
 59. Cooper DS. The side effects of antithyroid drugs. *Endocrinologist* 1999;9: 457–78. [[CrossRef](#)]
 60. Rivkees SA, Stephenson K, Dinauer C. Adverse events associated with methimazole therapy

- of graves disease in children. *Int J Pediatr Endocrinol* 2010;176970. [[Medline](#)] [[CrossRef](#)]
61. Hamburger JI. Management of hyperthyroidism in children and adolescents. *J Clin Endocrinol Metab* 1985;60: 1019–24. [[Medline](#)] [[CrossRef](#)]
 62. Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A, Hamada N, Working Group of the Japan Thyroid Association for the Guideline of the Treatment of Graves Disease. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves disease. *J Clin Endocrinol Metab* 2007;92: 2157–62. [[Medline](#)] [[CrossRef](#)]
 63. Gunton JE, Stiel J, Caterson RJ, McElduff A. Clinical case seminar: Anti-thyroid drugs and antineutrophil cytoplasmic antibody positive vasculitis. A case report and review of the literature. *J Clin Endocrinol Metab* 1999;84: 13–6. [[Medline](#)] [[CrossRef](#)]
 64. Sato H, Hattori M, Fujieda M, Sugihara S, Inomata H, Hoshi M, *et al.* High prevalence of antineutrophil cytoplasmic antibody positivity in childhood onset Graves disease treated with propylthiouracil. *J Clin Endocrinol Metab* 2000;85: 4270–3. [[Medline](#)]
 65. Noh JY, Yasuda S, Sato S, Matsumoto M, Kunii Y, Noguchi Y, *et al.* Clinical characteristics of myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis caused by antithyroid drugs. *J Clin Endocrinol Metab* 2009;94: 2806–11. [[Medline](#)] [[CrossRef](#)]
 66. Chen YX, Zhang W, Chen XN, Yu HJ, Ni LY, Xu J, *et al.* Propylthiouracil-induced antineutrophil cytoplasmic antibody (ANCA)-associated renal vasculitis versus primary ANCA-associated renal vasculitis: a comparative study. *J Rheumatol* 2012;39: 558–63. [[Medline](#)] [[CrossRef](#)]
 67. Mandel SJ, Brent GA, Larsen PR. Review of antithyroid drug use during pregnancy and report of a case of aplasia cutis. *Thyroid* 1994;4: 129–33. [[Medline](#)] [[CrossRef](#)]
 68. Yoshihara A, Noh J, Yamaguchi T, Ohye H, Sato S, Sekiya K, *et al.* Treatment of graves disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. *J Clin Endocrinol Metab* 2012;97: 2396–403. [[Medline](#)] [[CrossRef](#)]
 69. Dötsch J, Rascher W, Dörr HG. Graves disease in childhood: a review of the options for diagnosis and treatment. *Paediatr Drugs* 2003;5: 95–102. [[Medline](#)] [[CrossRef](#)]
 70. Dötsch J, Siebler T, Hauffa BP, Doeker B, Andler W, Bettendorf M, *et al.* Diagnosis and management of juvenile hyperthyroidism in Germany: a retrospective multicenter study. *J Pediatr Endocrinol Metab* 2000;13: 879–85. [[Medline](#)] [[CrossRef](#)]
 71. Mussa GC, Corrias A, Silvestro L, Battan E, Mostert M, Mussa F, *et al.* Factors at onset predictive of lasting remission in pediatric patients with Graves disease followed for at least three years. *J Pediatr Endocrinol Metab* 1999;12: 537–41. [[Medline](#)] [[CrossRef](#)]
 72. Slyper AH, Wyatt D, Boudreau C. Effective methimazole dose for childhood Graves disease and use of free triiodothyronine combined with concurrent thyroid-stimulating hormone level to identify mild hyperthyroidism and delayed pituitary recovery. *J Pediatr Endocrinol Metab* 2005;18: 597–602. [[Medline](#)] [[CrossRef](#)]
 73. Maia AL, Scheffel RS, Meyer EL, Mazeto GM, Carvalho GA, Graf H, *et al.* Brazilian Society of Endocrinology and Metabolism. The Brazilian consensus for the diagnosis and treatment of hyperthyroidism: recommendations by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism. *Arq Bras Endocrinol Metabol* 2013;57: 205–32. [[Medline](#)] [[CrossRef](#)]
 74. Kaguelidou F, Carel JC, Léger J. Graves disease in childhood: advances in management with antithyroid drug therapy. *Horm Res* 2009;71: 310–7. [[Medline](#)] [[CrossRef](#)]
 75. Stafford D, Vaidyanathan P, Kaplowitz P. Children with hyperthyroidism younger than age 7 require higher mg/kg doses of methimazole to normalize free T4 compared to older children. *J Pediatr Endocrinol Metab* 2015;28: 1339–42. [[Medline](#)] [[CrossRef](#)]
 76. Shulman DI, Muhar I, Jorgensen EV, Diamond FB, Bercu BB, Root AW. Autoimmune hyperthyroidism in prepubertal children and adolescents: comparison of clinical and biochemical features at diagnosis and responses to medical therapy. *Thyroid* 1997;7: 755–60. [[Medline](#)] [[CrossRef](#)]

77. Vitti P, Rago T, Chiovato L, Pallini S, Santini F, Fiore E, *et al.* Clinical features of patients with Graves disease undergoing remission after antithyroid drug treatment. *Thyroid* 1997;7: 369–75. [[Medline](#)] [[CrossRef](#)]
78. Benker G, Reinwein D, Kahaly G, Tegler L, Alexander WD, Fassbinder J, *et al.* The European Multicentre Trial Group of the Treatment of Hyperthyroidism with Antithyroid Drugs. Is there a methimazole dose effect on remission rate in Graves disease? Results from a long-term prospective study. *Clin Endocrinol (Oxf)* 1998;49: 451–7. [[Medline](#)] [[CrossRef](#)]
79. Michelangeli V, Poon C, Taft J, Newnham H, Topliss D, Colman P. The prognostic value of thyrotropin receptor antibody measurement in the early stages of treatment of Graves disease with antithyroid drugs. *Thyroid* 1998;8: 119–24. [[Medline](#)] [[CrossRef](#)]
80. Jafarzadeh A, Poorgholami M, Izadi N, Nemati M, Rezayati M. Immunological and hematological changes in patients with hyperthyroidism or hypothyroidism. *Clin Invest Med* 2010;33: E271–9. [[Medline](#)]
81. Kubota S, Amino N, Matsumoto Y, Ikeda N, Morita S, Kudo T, *et al.* Serial changes in liver function tests in patients with thyrotoxicosis induced by Graves disease and painless thyroiditis. *Thyroid* 2008;18: 283–7. [[Medline](#)] [[CrossRef](#)]
82. Sarinnapakorn V, Noppavetchwich P, Sunthorntepwarakul T, Deerochanawong C, Ngongamrut S. Abnormal liver function test in Graves disease: a prospective study of comparison between the hyperthyroid state and the euthyroid state. *J Med Assoc Thai* 2011;94(Suppl 2): S11–6. [[Medline](#)]
83. Sato S, Noh JY, Sato S, Suzuki M, Yasuda S, Matsumoto M, *et al.* Comparison of efficacy and adverse effects between methimazole 15 mg+inorganic iodine 38 mg/day and methimazole 30 mg/day as initial therapy for Graves disease patients with moderate to severe hyperthyroidism. *Thyroid* 2015;25: 43–50. [[Medline](#)] [[CrossRef](#)]
84. Reinwein D, Benker G, Lazarus JH, Alexander WD, European Multicenter Study Group on Antithyroid Drug Treatment. A prospective randomized trial of antithyroid drug dose in Graves disease therapy. *J Clin Endocrinol Metab* 1993;76: 1516–21. [[Medline](#)]
85. Takata K, Kubota S, Fukata S, Kudo T, Nishihara E, Ito M, *et al.* Methimazole-induced agranulocytosis in patients with Graves disease is more frequent with an initial dose of 30 mg daily than with 15 mg daily. *Thyroid* 2009;19: 559–63. [[Medline](#)] [[CrossRef](#)]
86. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137: 715–25. [[Medline](#)] [[CrossRef](#)]
87. Satoh M, Aso K, Nakayama T, Matsuura H, Ohara A, Tatenno A. Three patients with Graves' disease receiving long-term potassium iodide treatment. *J Jpn Pediatr Soc* 2010;114: 1713–7.
88. Okamura K, Sato K, Fujikawa M, Bandai S, Ikenoue H, Kitazono T. Remission after potassium iodide therapy in patients with Graves hyperthyroidism exhibiting thionamide-associated side effects. *J Clin Endocrinol Metab* 2014;99: 3995–4002. [[Medline](#)] [[CrossRef](#)]
89. Uchida T, Goto H, Kasai T, Komiya K, Takeno K, Abe H, *et al.* Therapeutic effectiveness of potassium iodine in drug-naïve patients with Graves disease: a single-center experience. *Endocrine* 2014;47: 506–11. [[Medline](#)] [[CrossRef](#)]
90. Takata K, Amino N, Kubota S, Sasaki I, Nishihara E, Kudo T, *et al.* Benefit of short-term iodide supplementation to antithyroid drug treatment of thyrotoxicosis due to Graves disease. *Clin Endocrinol (Oxf)* 2010;72: 845–50. [[Medline](#)] [[CrossRef](#)]
91. Jeong KU, Lee HS, Hwang JS. Effects of short-term potassium iodide treatment for thyrotoxicosis due to Graves disease in children and adolescents. *Ann Pediatr Endocrinol Metab* 2014;19: 197–201. [[Medline](#)] [[CrossRef](#)]
92. Raza J, Hindmarsh PC, Brook CG. Thyrotoxicosis in children: thirty years experience. *Acta Paediatr* 1999;88: 937–41. [[Medline](#)] [[CrossRef](#)]
93. Abraham P, Avenell A, Park CM, Watson WA, Bevan JS. A systematic review of drug therapy for Graves hyperthyroidism. *Eur J Endocrinol* 2005;153: 489–98. [[Medline](#)] [[CrossRef](#)]
94. Razvi S, Vaidya B, Perros P, Pearce SH.

- What is the evidence behind the evidence-base? The premature death of block-replace antithyroid drug regimens for Graves disease. *Eur J Endocrinol* 2006;154: 783–6. [[Medline](#)] [[CrossRef](#)]
95. Abraham P, Avenell A, Watson WA, Park CM, Bevan JS. Antithyroid drug regimen for treating Graves hyperthyroidism. *Cochrane Database Syst Rev* 2004; CD003420. [[Medline](#)]
 96. Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. *Cochrane Database Syst Rev* 2010; CD003420. [[Medline](#)]
 97. Solomon BL, Wartofsky L, Burman KD. Adjunctive cholestyramine therapy for thyrotoxicosis. *Clin Endocrinol (Oxf)* 1993;38: 39–43. [[Medline](#)] [[CrossRef](#)]
 98. Heemstra KA, Toes RE, Sepers J, Pereira AM, Corssmit EP, Huizinga TW, *et al.* Rituximab in relapsing Graves disease, a phase II study. *Eur J Endocrinol* 2008;159: 609–15. [[Medline](#)] [[CrossRef](#)]
 99. Tsuyusaki T. Prognosis of children with Graves' disease treated with Antithyroid Drug. *Chiba Med J* 1989;65: 227–34 (in Japanese).
 100. Lippe BM, Landaw EM, Kaplan SA. Hyperthyroidism in children treated with long term medical therapy: twenty-five percent remission every two years. *J Clin Endocrinol Metab* 1987;64: 1241–5. [[Medline](#)] [[CrossRef](#)]
 101. Konishi T, Okamoto Y, Ueda M, Fukuda Y, Harusato I, Tsukamoto Y, *et al.* Drug discontinuation after treatment with minimum maintenance dose of an antithyroid drug in Graves disease: a retrospective study on effects of treatment duration with minimum maintenance dose on lasting remission. *Endocr J* 2011;58: 95–100. [[Medline](#)] [[CrossRef](#)]
 102. Weetman AP. Graves hyperthyroidism: how long should antithyroid drug therapy be continued to achieve remission? *Nat Clin Pract Endocrinol Metab* 2006;2: 2–3. [[Medline](#)] [[CrossRef](#)]
 103. Glaser NS, Styne DM. Predictors of early remission of hyperthyroidism in children. *J Clin Endocrinol Metab* 1997;82: 1719–26. [[Medline](#)]
 104. Maugendre D, Gatel A, Campion L, Massart C, Guilhem I, Lorcy Y, *et al.* Antithyroid drugs and Graves diseaseprospective randomized assessment of long-term treatment. *Clin Endocrinol (Oxf)* 1999;50: 127–32. [[Medline](#)] [[CrossRef](#)]
 105. Bauer AJ. Approach to the pediatric patient with Graves disease: when is definitive therapy warranted? *J Clin Endocrinol Metab* 2011;96: 580–8. [[Medline](#)] [[CrossRef](#)]
 106. Rivkees SA. Pediatric Graves disease: management in the post-propylthiouracil Era. *Int J Pediatr Endocrinol* 2014;2014: 10 [[CrossRef](#)]. [[Medline](#)]
 107. Léger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C, French Childhood Graves Disease Study Group. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves disease: national long-term cohort study. *J Clin Endocrinol Metab* 2012;97: 110–9. [[Medline](#)] [[CrossRef](#)]
 108. Hiraiwa T, Ito M, Imagawa A, Takamatsu J, Kuma K, Miyauchi A, *et al.* Restriction of dietary Iodine does not ameliorate the early effect of anti-thyroid drug therapy for Graves disease in an area of excessive iodine intake. *J Endocrinol Invest* 2006;29: 380–4. [[Medline](#)] [[CrossRef](#)]
 109. Park SM, Cho YY, Joung JY, Sohn SY, Kim SW, Chung JH. Excessive iodine intake does not increase the recurrence rate of graves disease after withdrawal of the antithyroid drug in an iodine-replete area. *Eur Thyroid J* 2015;4: 36–42. [[Medline](#)] [[CrossRef](#)]
 110. Tamai H, Takaichi Y, Morita T, Komaki G, Matsubayashi S, Kuma K, *et al.* Methimazole-induced agranulocytosis in Japanese patients with Graves disease. *Clin Endocrinol (Oxf)* 1989;30: 525–30. [[Medline](#)] [[CrossRef](#)]
 111. Cooper DS, Goldminz D, Levin AA, Ladenson PW, Daniels GH, Molitch ME, *et al.* Agranulocytosis associated with antithyroid drugs. Effects of patient age and drug dose. *Ann Intern Med* 1983;98: 26–9. [[Medline](#)] [[CrossRef](#)]
 112. Hamerschlak N, Maluf E, Biasi Cavalcanti A, Avezum Júnior A, Eluf-Neto J, Passeto Falcão R, *et al.* Incidence and risk factors for agranulocytosis in Latin American countries the Latin Study: a multicenter study. *Eur J Clin Pharmacol* 2008;64: 921–9. [[Medline](#)] [[CrossRef](#)]
 113. Tajiri J, Noguchi S, Murakami N. Usefulness of granulocyte count measurement four hours

- after injection of granulocyte colony-stimulating factor for detecting recovery from antithyroid drug-induced granulocytopenia. *Thyroid* 1997;7: 575–8. [[Medline](#)] [[CrossRef](#)]
114. Tajiri J, Noguchi S. Antithyroid drug-induced agranulocytosis: how has granulocyte colony-stimulating factor changed therapy? *Thyroid* 2005;15: 292–7. [[Medline](#)] [[CrossRef](#)]
115. Rivkees SA, Szarfman A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. *J Clin Endocrinol Metab* 2010;95: 3260–7. [[Medline](#)] [[CrossRef](#)]
116. Williams KV, Nayak S, Becker D, Reyes J, Burmeister LA. Fifty years of experience with propylthiouracil-associated hepatotoxicity: what have we learned? *J Clin Endocrinol Metab* 1997;82: 1727–33. [[Medline](#)]
117. Harada S, Arisaka O, Yokoya S, Amemiya S, Tanaka T, Hasegawa T, *et al.* Difference in Japan-U.S. correspondence about the serious liver damage of childhood Graves' disease with the antithyroid drug. The 43rd annual meeting of the Japanese Society for Pediatric Endocrinology 2009. p. 71(abstract) (in Japanese).
118. Takano T, Okazaki M, Kagimoto S, Joh K, Ohishi T, Kohda N, *et al.* The 10-year-old boy with Graves' disease that developed serious hepatitis by Propylthiouracil. *J Saitama Med Soc* 2000;35: 467–70.
119. Umemoto M, Sawada H, Sugiyama K, Higashigawa M, Sakurai M. Propylthiouracil-induced hepatic failure with fatal outcome. *Clin Pediatr Endocrinol* 1997;6: 73–5. [[CrossRef](#)]
120. Otsuka F, Noh JY, Chino T, Shimizu T, Mukasa K, Ito K, *et al.* Hepatotoxicity and cutaneous reactions after antithyroid drug administration. *Clin Endocrinol (Oxf)* 2012;77: 310–5. [[Medline](#)] [[CrossRef](#)]
121. Glaser NS, Styne DM, Organization of Pediatric Endocrinologists of Northern California Collaborative Graves Disease Study Group. Predicting the likelihood of remission in children with Graves disease: a prospective, multicenter study. *Pediatrics* 2008;121: e481–8. [[Medline](#)] [[CrossRef](#)]
122. Poyrazoğlu S, Saka N, Bas F, Isguven P, Dogu A, Turan S, *et al.* Evaluation of diagnosis and treatment results in children with Graves disease with emphasis on the pubertal status of patients. *J Pediatr Endocrinol Metab* 2008;21: 745–51. [[Medline](#)] [[CrossRef](#)]
123. Kaguelidou F, Alberti C, Castanet M, Guittény MA, Czernichow P, Léger J, French Childhood Graves Disease Study Group. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. *J Clin Endocrinol Metab* 2008;93: 3817–26. [[Medline](#)] [[CrossRef](#)]
124. Takasu N, Yamashiro K, Komiya I, Ochi Y, Sato Y, Nagata A. Remission of Graves hyperthyroidism predicted by smooth decreases of thyroid-stimulating antibody and thyrotropin-binding inhibitor immunoglobulin during antithyroid drug treatment. *Thyroid* 2000;10: 891–6. [[Medline](#)] [[CrossRef](#)]
125. Quadbeck B, Hoermann R, Roggenbuck U, Hahn S, Mann K, Janssen OE, Basedow Study Group. Sensitive thyrotropin and thyrotropin-receptor antibody determinations one month after discontinuation of antithyroid drug treatment as predictors of relapse in Graves disease. *Thyroid* 2005;15: 1047–54. [[Medline](#)] [[CrossRef](#)]
126. Bhadada S, Bhansali A, Velayutham P, Masoodi SR. Juvenile hyperthyroidism: an experience. *Indian Pediatr* 2006;43: 301–7. [[Medline](#)]
127. Gastaldi R, Poggi E, Mussa A, Weber G, Vigone MC, Salerno M, *et al.* Graves disease in children: thyroid-stimulating hormone receptor antibodies as remission markers. *J Pediatr* 2014;164: 1189–94.e1. [[Medline](#)] [[CrossRef](#)]
128. Gruñeiro-Papendieck L, Chiesa A, Finkielstain G, Heinrich JJ. Pediatric Graves disease: outcome and treatment. *J Pediatr Endocrinol Metab* 2003;16: 1249–55. [[Medline](#)]
129. Somnuk PH, Pusuwan P, Likitmaskul S, Santiprabhob J, Sawathiparnich P. Treatment outcome of Graves disease in Thai children. *J Med Assoc Thai* 2007;90: 1815–20. [[Medline](#)]
130. Brownlie BE, Hunt PJ, Turner JG. Juvenile thyrotoxicosis South Island, New Zealand experience with long-term outcome. *N Z Med J* 2010;123: 23–31. [[Medline](#)]
131. Barrio R, López-Capapé M, Martínez-Badás I, Carrillo A, Moreno JC, Alonso M. Graves disease in children and adolescents: response to long-term treatment. *Acta Paediatr* 2005;94: 1583–9.

- [Medline] [CrossRef]
132. Kashiwai T, Hidaka Y, Takano T, Tatsumi KI, Izumi Y, Shimaoka Y, *et al.* Practical treatment with minimum maintenance dose of anti-thyroid drugs for prediction of remission in Graves disease. *Endocr J* 2003;50: 45–9. [Medline] [CrossRef]
133. Harada S. Studies on TSH receptor antibodies (TRAb) in patients with juvenile Graves' disease: clinical studies on usefulness of TRAb determinations. *J Jpn Pediatr Soc* 1991;95: 1751–7 (in Japanese).
134. Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tørring O. TSH-receptor autoimmunity in Graves disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. *Eur J Endocrinol* 2008;158: 69–75. [Medline] [CrossRef]
135. Okamoto Y, Tanigawa S, Ishikawa K, Hamada N. TSH receptor antibody measurements and prediction of remission in Graves disease patients treated with minimum maintenance doses of antithyroid drugs. *Endocr J* 2006;53: 467–72. [Medline] [CrossRef]
136. Takasu N, Akamine H, Komiya I, Yamada T. Simple and reliable method for predicting the remission of Graves disease: revised triiodothyronine-suppression test, indexed by serum thyroxine. *J Endocrinol Invest* 1995;18: 288–94. [Medline] [CrossRef]
137. Sugino K, Ito K, Mimura T, Fukunari N, Nagahama M, Ito K. Surgical treatment of Graves disease in children. *Thyroid* 2004;14: 447–52. [Medline] [CrossRef]
138. Lee JA, Grumbach MM, Clark OH. The optimal treatment for pediatric Graves disease is surgery. *J Clin Endocrinol Metab* 2007;92: 801–3. [Medline] [CrossRef]
139. Sosa JA, Tuggle CT, Wang TS, Thomas DC, Boudourakis L, Rivkees S, *et al.* Clinical and economic outcomes of thyroid and parathyroid surgery in children. *J Clin Endocrinol Metab* 2008;93: 3058–65. [Medline] [CrossRef]
140. Tuggle CT, Roman SA, Wang TS, Boudourakis L, Thomas DC, Udelsman R, *et al.* Pediatric endocrine surgery: who is operating on our children? *Surgery* 2008;144: 869–77, discussion 877. [Medline] [CrossRef]
141. Sherman J, Thompson GB, Lteif A, Schwenk WF 2nd, van Heerden J, Farley DR, *et al.* Surgical management of Graves disease in childhood and adolescence: an institutional experience. *Surgery* 2006;140: 1056–61, discussion 1061–2. [Medline] [CrossRef]
142. Bergman P, Auldlist AW, Cameron F. Review of the outcome of management of Graves disease in children and adolescents. *J Paediatr Child Health* 2001;37: 176–82. [Medline] [CrossRef]
143. Sugino K, Ito K, Nagahama M, Kitagawa W, Shibuya H, Ito K. Surgical management of Graves disease -10-year prospective trial at a single institution. *Endocr J* 2008;55: 161–7. [Medline] [CrossRef]
144. Miccoli P, Vitti P, Rago T, Iacconi P, Bartalena L, Bogazzi F, *et al.* Surgical treatment of Graves disease: subtotal or total thyroidectomy? *Surgery* 1996;120: 1020–4, discussion 1024–5. [Medline] [CrossRef]
145. Rudberg C, Johansson H, Akerström G, Tuvemo T, Karlsson FA. Graves disease in children and adolescents. Late results of surgical treatment. *Eur J Endocrinol* 1996;134: 710–5. [Medline] [CrossRef]
146. Feliciano DV, Lyons JD. Thyroidectomy is optimal treatment for Graves disease. *J Am Coll Surg* 2011;212: 714–20, discussion 720–1. [Medline] [CrossRef]
147. Liu J, Bargren A, Schaefer S, Chen H, Sippel RS. Total thyroidectomy: a safe and effective treatment for Graves disease. *J Surg Res* 2011;168: 1–4. [Medline] [CrossRef]
148. Cheetham TD, Hughes IA, Barnes ND, Wraight EP. Treatment of hyperthyroidism in young people. *Arch Dis Child* 1998;78: 207–9. [Medline] [CrossRef]
149. Peters H, Fischer C, Bogner U, Reiners C, Schleusener H. Reduction in thyroid volume after radioiodine therapy of Graves hyperthyroidism: results of a prospective, randomized, multicentre study. *Eur J Clin Invest* 1996;26: 59–63. [Medline] [CrossRef]
150. Peters H, Fischer C, Bogner U, Reiners C, Schleusener H. Treatment of Graves hyperthyroidism with radioiodine: results of a prospective randomized study. *Thyroid* 1997;7:

- 247–51. [\[Medline\]](#) [\[CrossRef\]](#)
151. Rivkees SA, Sklar C, Freemark M. Clinical review 99: The management of Graves disease in children, with special emphasis on radioiodine treatment. *J Clin Endocrinol Metab* 1998;83: 3767–76. [\[Medline\]](#)
152. Kraiem Z, Newfield RS. Graves disease in childhood. *J Pediatr Endocrinol Metab* 2001;14: 229–43. [\[Medline\]](#) [\[CrossRef\]](#)
153. Ma C, Kuang A, Xie J, Liu G. Radioiodine treatment for pediatric Graves disease. *Cochrane Database Syst Rev* 2008; CD006294. [\[Medline\]](#)
154. Rivkees SA, Dinauer C. An optimal treatment for pediatric Graves disease is radioiodine. *J Clin Endocrinol Metab* 2007;92: 797–800. [\[Medline\]](#) [\[CrossRef\]](#)
155. Ogawa T, Goshi K, Tajiri J. Radioactive iodine therapy for patients with Graves' disease aged 18 or younger. *J Jpn Pediatr Soc* 2008;112: 15–21 (in Japanese).
156. Okubo T. The determination of thyroid weight in vivo with the scintigram. *Jpn J Radiol* 1959;19: 120–8 (in Japanese).
157. Ma C, Kuang A, Xie J, Liu G. Radioiodine treatment for pediatric Graves' disease. *Cochrane Database Syst Rev* 2008; CD006294. [\[Medline\]](#)
158. Levy WJ, Schumacher OP, Gupta M. Treatment of childhood Graves disease. A review with emphasis on radioiodine treatment. *Cleve Clin J Med* 1988;55: 373–82. [\[Medline\]](#) [\[CrossRef\]](#)
159. Freitas JE, Swanson DP, Gross MD, Sisson JC. Iodine-131: optimal therapy for hyperthyroidism in children and adolescents? *J Nucl Med* 1979;20: 847–50. [\[Medline\]](#)
160. Kalinyak JE, McDougall IR. How should the dose of iodine-131 be determined in the treatment of Graves hyperthyroidism? *J Clin Endocrinol Metab* 2003;88: 975–7. [\[Medline\]](#) [\[CrossRef\]](#)
161. Zantut-Wittmann DE, Ramos CD, Santos AO, Lima MM, Panzan AD, Facuri FV, *et al.* High pre-therapy ^{99m}Tc]pertechnetate thyroid uptake, thyroid size and thyrostatic drugs: predictive factors of failure in [¹³¹I]iodide therapy in Graves disease. *Nucl Med Commun* 2005;26: 957–63. [\[Medline\]](#) [\[CrossRef\]](#)
162. Nebesio TD, Siddiqui AR, Pescovitz OH, Eugster EA. Time course to hypothyroidism after fixed-dose radioablation therapy of Graves disease in children. *J Pediatr* 2002;141: 99–103. [\[Medline\]](#) [\[CrossRef\]](#)
163. Ueda D. Normal volume of the thyroid gland in children. *J Clin Ultrasound* 1990;18: 455–62. [\[Medline\]](#) [\[CrossRef\]](#)
164. Rivkees SA. Graves disease therapy in children: truth and inevitable consequences. *J Pediatr Endocrinol Metab* 2007;20: 953–5. [\[Medline\]](#)
165. Kadmon PM, Noto RB, Boney CM, Goodwin G, Gruppuso PA. Thyroid storm in a child following radioactive iodine (RAI) therapy: a consequence of RAI versus withdrawal of antithyroid medication. *J Clin Endocrinol Metab* 2001;86: 1865–7. [\[Medline\]](#) [\[CrossRef\]](#)
166. Bonnema SJ, Bennedbaek FN, Gram J, Veje A, Marving J, Hegedus L. Resumption of methimazole after ¹³¹I therapy of hyperthyroid diseases: effect on thyroid function and volume evaluated by a randomized clinical trial. *Eur J Endocrinol* 2003;149: 485–92. [\[Medline\]](#) [\[CrossRef\]](#)
167. Nakajo M, Tsuchimochi S, Tanabe H, Nakabeppu Y, Jinguji M. Three basic patterns of changes in serum thyroid hormone levels in Graves disease during the one-year period after radioiodine therapy. *Ann Nucl Med* 2005;19: 297–308. [\[Medline\]](#) [\[CrossRef\]](#)
168. Rivkees SA, Cornelius EA. Influence of iodine-131 dose on the outcome of hyperthyroidism in children. *Pediatrics* 2003;111: 745–9. [\[Medline\]](#) [\[CrossRef\]](#)
169. Cury AN, Meira VT, Monte O, Marone M, Scalissi NM, Kochi C, *et al.* Clinical experience with radioactive iodine in the treatment of childhood and adolescent Graves disease. *Endocr Connect* 2012;2: 32–7. [\[Medline\]](#) [\[CrossRef\]](#)
170. Sheline GE, Lindsay S, McCormack KR, Galante M. Thyroid nodules occurring late after treatment of thyrotoxicosis with radioiodine. *J Clin Endocrinol Metab* 1962;22: 8–18. [\[Medline\]](#) [\[CrossRef\]](#)
171. Boice JD Jr. Thyroid disease 60 years after Hiroshima and 20 years after Chernobyl. *JAMA* 2006;295: 1060–2. [\[Medline\]](#) [\[CrossRef\]](#)
172. Boice JD Jr. Radiation-induced thyroid cancer: what's new? *J Natl Cancer Inst* 2005;97:

- 703–5. [\[Medline\]](#) [\[CrossRef\]](#)
173. Dobyns BM, Sheline GE, Workman JB, Tompkins EA, McConahey WM, Becker DV. Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the cooperative thyrotoxicosis therapy follow-up study. *J Clin Endocrinol Metab* 1974;38: 976–98. [\[Medline\]](#) [\[CrossRef\]](#)
174. Boice JD Jr. Radiation and thyroid cancer: what more can be learned? *Acta Oncol* 1998;37: 321–4. [\[Medline\]](#) [\[CrossRef\]](#)
175. Dolphin GW. The risk of thyroid cancers following irradiation. *Health Phys* 1968;15: 219–28. [\[Medline\]](#) [\[CrossRef\]](#)
176. Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, *et al.* Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. *Lancet* 2005;365: 2014–23. [\[Medline\]](#) [\[CrossRef\]](#)
177. Davis S, Kopecky KJ, Hamilton TE, Onstad L, Hanford Thyroid Disease Study Team. Thyroid neoplasia, autoimmune thyroiditis, and hypothyroidism in persons exposed to iodine 131 from the hanford nuclear site. *JAMA* 2004;292: 2600–13. [\[Medline\]](#) [\[CrossRef\]](#)
178. Dickman PW, Holm LE, Lundell G, Boice JD Jr, Hall P. Thyroid cancer risk after thyroid examination with 131I: a population-based cohort study in Sweden. *Int J Cancer* 2003;106: 580–7. [\[Medline\]](#) [\[CrossRef\]](#)
179. Toohey RE, Stabin MG, Watson EE. The AAPM/RSNA physics tutorial for residents: internal radiation dosimetry: principles and applications. *Radiographics* 2000;20: 533–46, quiz 531–2. [\[Medline\]](#) [\[CrossRef\]](#)
180. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, Board on Radiation Effects, Research Division on Earth and Life Studies, National Research Council of the National Academies. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII-Phase 2*. Washington DC.: National Academies Press. 2006.
181. Read CH Jr, Tansey MJ, Menda Y. A 36-year retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves patients. *J Clin Endocrinol Metab* 2004;89: 4229–33. [\[Medline\]](#) [\[CrossRef\]](#)
182. Turner N, Driver I, Salotti JA, Pearce MS, Cheetham T. Increasing use of radioiodine in young people with thyrotoxicosis in Great Britain. *Eur J Endocrinol* 2012;167: 715–8. [\[Medline\]](#) [\[CrossRef\]](#)
183. Shore RE. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. *Radiat Res* 1992;131: 98–111. [\[Medline\]](#) [\[CrossRef\]](#)
184. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, *et al.* Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 1995;141: 259–77. [\[Medline\]](#) [\[CrossRef\]](#)
185. Imaizumi M, Usa T, Tominaga T, Neriishi K, Akahoshi M, Nakashima E, *et al.* Radiation dose-response relationships for thyroid nodules and autoimmune thyroid diseases in Hiroshima and Nagasaki atomic bomb survivors 5558 years after radiation exposure. *JAMA* 2006;295: 1011–22. [\[Medline\]](#) [\[CrossRef\]](#)
186. Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, *et al.* Japan Thyroid Association. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. *Thyroid* 2012;22: 661–79. [\[Medline\]](#) [\[CrossRef\]](#)
187. Agus MS. Endocrine emergencies. In: Fleisher GR, Ludwig S editors. *Textbook of Pediatric Emergency Medicine* 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010. p. 758-82.
188. Wartofsky L. Thyrotoxic storm. In: Braverman LE, Cooper D, editors. *Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text* 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012. p.481-6.
189. Hecht T, Brand J, Vlaho S. Encephalopathy and sinustachycardia in childhood a possible differential diagnosis. *J Pediatr Endocrinol Metab* 2012;25: 149–51. [\[Medline\]](#) [\[CrossRef\]](#)
190. Minamitani K, Ogita J, Kurosaki T. The 4-year-old thyroid crisis girl suspected of acute encephalopathy. *J Jpn Thyroid Assoc* 2014;5: 50–2 (in Japanese).
191. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am* 1993;22: 263–77. [\[Medline\]](#)