J Endocrinol Invest (2016) 39:1247–1257
DOI 10.1007/s40618-016-0477-x

SHORT REVIEW

Controversies in the management of Graves' disease in children

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Received: 19 April 2016 / Accepted: 22 April 2016 / Published online: 6 May 2016

Abstract Graves' disease (GD) is the most prevalent cause of thyrotoxicosis in children. Because spontaneous and lasting resolution of this condition occurs in only a minority of patients, most pediatric patients with GD will need radioactive iodine treatment (^{131}I) or thyroidectomy. Whereas the medication propylthiouracil (PTU) had been used in the past, only methimazole (MMI) should be now used in children, as PTU is associated with an unacceptable risk of liver failure. However, MMI may be associated minor and major side effects, which may be minimized using lower doses. An area of controversy involves the optimal duration of antithyroid drug (ATD) therapy. For some children, the prolonged use of antithyroid drugs is a valid approach, but for most, this will not increase the chance of remission. When ^{131}I is administered, dosages should be greater than 150 uCi/gm of thyroid tissue, with higher dosages needed for larger glands. Considering that there will be low-level whole body radiation exposure associated with ^{131}I, this treatment is viewed as controversial by some and should be avoided in young children. When surgery is performed, near-total or total thyroidectomy is the recommended procedure. Complications for thyroidectomy in children are considerably higher than in adults. Thus, an experienced thyroid surgeon is needed when children have surgery. Overall, when different treatment options for GD are considered, the benefits, risks and viewpoints of the family need to be considered and discussed in full.

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Keywords Thyroid · Hyperthyroidism · Methimazole · Propylthiouracil · Radioactive iodine · Thyroidectomy · Hepatotoxicity

Graves' disease

Graves' disease (GD) is the most common cause of hyperthyroidism in children and affects 1 in 10,000 children [1]. An autoimmune disorder GD is due to thyroid gland stimulation by thyroid receptor antibodies [TRAbs or thyroid-stimulating immunoglobulins (TSI)] and involves genetic factors [2, 3]. Hyperthyroidism can exert profound adverse effects on children, including excessive physical activity, tremor, tachycardia, flushing, palpitations, weight loss, accelerated linear growth, reduced bone mineralization and poor school performance [4]. In comparison with adults [5–7], eye disease occurs in the minority of pediatric patients with GD, and when it presents, is usually mild [4].

Over the past several years, additional outcome data have become available [8–12] to complement older studies looking at spontaneous remission rates of children with GD [13–17]. Collectively, these studies show that the majority of pediatric patients with GD will not undergo spontaneous remission even after many years of antithyroid drug (ATD) therapy. But, it may be possible to distinguish those children with a greater chance of spontaneous remission from those in whom definitive therapy will be needed to achieve care. That said most pediatric patients will require either radioactive iodine (^{131}I) or surgery [4, 18–21]. Importantly, each of these treatment approaches is associated with specific risks that need to be considered. Each of the therapeutic approaches involves controversial aspects, which are addressed in this report.

Controversies with antithyroid drugs

ATDs act by inhibiting oxidation and organic binding of thyroid iodide to impair thyroid hormone production and include methimazole (MMI) and propylthiouracil (PTU) [22]. MMI is tenfold to 20-fold more potent than PTU and has a longer half-life [22]. These medications do not cure the hyperthyroid state; rather, they palliate the condition until spontaneous remission occurs or definitive therapy is rendered. Each of these medications is associated with adverse events that must be considered when prescribed. As such, prior to the initiation of drug therapy, a backup plan that takes into account the patient's age and treatment risks must be developed at therapy onset in the event that a toxic reaction occurs.

Because it takes one or 2 months until biochemical hyperthyroidism resolves on drug therapy [23], treatment with beta-blockers (propranolol, atenolol or metoprolol) can be used to control GD symptoms. Focusing on symptom control with beta-blockers also alleviates the perceived need for initial high-dose ATD therapy.

Which antithyroid drug should be used?

In 2008, Rivkees brought to public attention a number of serious complications associated with PTU therapy in children [24–26]. From 1990 to 2007, 23 PTU-related liver transplants took place, and 30 % of the PTU-related transplant recipients were children [24–26]. Based on prescribing data, the risk of PTU-induced liver failure leading to transplantation was estimated to be 1 in 2000 children [1].

PTU-induced liver injury occurs rapidly and is often irreversible [25, 27]. Thus, serial monitoring of transaminase levels in a child on PTU, is not viewed as useful in reducing the hepatotoxicity risk [1]. The only way to reduce the risks of PTU-related hepatotoxicity is to thus avoid the use of the medication. Reinforcing this notion, in April 2010, the US Food and Drug Administration issued a black box regarding the use of PTU stating that PTU should not be used in children [24].

PTU, though, may be needed in special circumstances [26]. These conditions include situations when neither prompt ^{131} I or surgical treatment is options in a patient who has had a toxic reaction to MMI, and ATD medication is necessary. In this setting, PTU use should only be short-term [26].

If PTU is prescribed, patients and guardians must be informed of the risk of liver failure and to be alert for signs and symptoms of liver abnormalities, including pruritus, jaundice, anorexia, light colored stools, dark urine and abdominal pain. If these symptoms develop, the patient should immediately stop the medication, a physician contacted and laboratory tests obtained to evaluate hepatic function and transaminase levels [26].

How should methimazole be used?

MMI is now the drug of choice for GD. The typical MMI doses described in published reports is 0.2–0.5 mg/kg per day and range from 0.1 to 1.0 mg/kg per day [3, 28–32]. However, as noted below, lower rather than higher doses should be considered. Although MMI is often prescribed in divided doses over the day, once a day dosing is usually sufficient [23] and is associated with better compliance than multiple daily doses [33].

MMI is available in 5, 10 and 20 mg tablets. When used in children, the following doses that are fractions of tablets can be used: infants, 1.25 mg per day; 1–5 years, 2.5–5.0 mg/day; 5–10 years, 5–10 mg/day; and 10–18 years, 10–20 mg/day (Table 1). Because the hyperthyroid state can be associated with low white cell counts and patients will be treated with a medication that can depress neutrophil levels, one should obtain a complete blood count at therapy onset [34]. In addition, we routinely obtain transaminase levels and liver function tests at therapy onset, to assess for premorbid liver disease, as we find that 1 % of our pediatric patients with GD have autoimmune hepatitis.

It is important to recognize that one does not need to use high doses at treatment onset. The response to ATDs influencing circulating thyroid hormone levels is not instantaneous, and several months are needed for thyroid hormone levels to normalize [20, 23]. Thyroid function tests should be obtained monthly after therapy onset. After T4 levels become normal, the MMI doses can be cut by half to maintain euthyroidism [35].

Rather than titrating the MMI dose lower when circulating thyroid hormone levels fall, some physicians prefer the block-and-replace approach and add levo-thyroxine while not changing the MMI dose. There is a greater risk of adverse events using block-and-replace versus dose reduction [35, 36]. Because there is a potential dose–response relationship for some MMI-related complications [37, 38], we prefer to use the lowest MMI dose

Table 1 Recommendations for the use of methimazole

Infants	1.25 mg per day
1–5 years	2.5–5.0 mg per day
5–10 years	5–10 mg per day
10–18 years	10–20 mg a day

Agranulocytosis and side effects appear to be dose-dependent

Thus, use low doses

Be sure to warn families about side effects

Immediately discontinue medication if child becomes ill

that achieves control, rather than the block-and-replace approach.

What are risks of methimazole?

Although MMI is the drug of choice for GD, MMI therapy is not without risks. Minor side effects may affect up to 20 % of children, and major side effects may occur in 1 % of children [12, 39]. The most common minor adverse side effects related to MMI are hives, arthralgia and neutropenia [12, 39]. Children may also develop major side effects, including agranulocytosis, Stevens–Johnson syndrome and vasculitis [39].

MMI adverse events most commonly occur within 6 months of therapy onset [12, 39]. Yet, children may develop adverse events more than 12 months after treatment onset. This potential risk highlights the need for constant vigilance while on therapy, an important consideration for those on prolonged ATD treatment.

Agranulocytosis is a potential serious ATD adverse event and occurs in 0.3 % of adults taking PTU or MMI [20, 40]. The agranulocytosis risk is dose-dependent and is rare [20, 40]. If an individual receiving MMI feels ill, becomes febrile or develops pharyngitis, MMI should be stopped immediately, a practitioner contacted and a complete blood cell count obtained.

Agranulocytosis typically develops in the first 100 days of therapy [20, 40]. As such, whereas it is tempting to treat GD with high doses of ATD therapy at onset to quickly control the hyperthyroid state, this heavy-handed approach should be avoided in our opinion. Rather, relatively lower doses of MMI should be used initially and symptoms managed with beta-blockers. Furthermore, the time to normalization of thyroid function tests is only modestly different in individuals treated with high vs. low ATD doses [23].

What is the optimal duration for ATD therapy?

The optimal duration for ATD therapy remains undefined, and it is controversial as to whether there is a role for extended ATD therapy. Based on available evidence [8, 13–17], prolonged ATD therapy will not result in an increased chance of remission for most children, whereas in others it may. As such, with the initial evaluation of a child with GD, practitioners should attempt to stratify children into two groups: those children with a 30–40 % change in remission with prolonged ATD therapy and those with a slim chance of spontaneous remission.

Prospective studies in adults show that if remission does not occur after 12–18 months of ATD therapy, there is a very low likelihood of remission occurring with prolonged therapy [41]. In a French study of 94 patients, following treatment for 6 or 18 months, remission rates were 42 and 62 %, respectively, after 2 years of treatment [42]. In 52 Spanish patients, following treatment for 12 or 24 months, remission rates were 46 and 54 %, respectively, 2 years after cessation of therapy [43] and at 5-years the relapse rate was 85 %. A study of 134 French patients found no benefit of 18 versus 43 months of treatment [44].

In the pediatric population, published data generally show that when ATDs are used for 1–2 years, remission rates are 15–30 %, and possibly up to 40 % in some children [8–17]. (Remission is defined as being either euthyroid or hypothyroid for 1 year or more after cessation of therapy.) Yet, looking closely at these data, one can distinguish patients with a greater likelihood of remission from those with a much lower chance following prolonged ATD therapy. The chance of remission after years of ATDs will be low if the thyroid gland is large (>2 times normal size for age), the child is young (<12 years), not Caucasian, serum TRAb/TSI levels are elevated, or the patient presents with profound hyperthyroidism at presentation (free $T_4 > 4$ ng/dL) [8, 9, 13, 14].

In adults, assessment of TRAb or TSI levels is useful in determining disease course and remission likelihood [45, 46]. This issue has been less studied in children. Consistent with the notion that GD will remit in only a small proportion of children, TRAb levels normalize after 24 months in only 18 % of pediatric patients on ATDs [3]. TRAb levels thus persist longer in children than in adults [3]. There are no data to show normalization of TRAb levels when patients are on ATDs for a longer time.

Rates of remission have been evaluated in several important studies. More than 25 years ago, Lippe and coworkers estimated that 25 % of children go into remission for every 2 years of treatment [16]. Of the 63 patients followed on ATDs, 36 (57 %) remitted after an average of 4 years of therapy [16]. Yet, there are no data to show if the patients who came off ATDs remained in remission [16].

Of more than 200 children with GD in Minnesota, 25 % were in remission after 1 year; 25 % after 2 years; 26 % after 4 years; and 15 % after 10 years. In addition, 30 % of the boys and girls who went into remission had disease recurrence [15]. Thus, overall remission rates, even after 10 years of treatment, were about 15 %.

When 184 pediatric children in California were followed for up to 4 years, the overall remission rate was 23 % [13]. After 1 year of ATDs, 10 % were in remission; after 2 years, 14 % were in remission; after 3 years, 20 % were in remission; and after 4 years, 23 % were in remission.

In a study of 32 prepubertal vs. 68 pubertal children with GD, remission occurred in 17 % of prepubertal children treated for 6 years versus 30 % of pubertal children [17]. In another report with pre- and post-pubertal cohorts, remission occurred in 28 % of children [47], but the time to remission was three times longer in the prepubertal

children than pubertal children [47]. Adverse reactions to ATDs occurred with greater frequency in prepubertal children (71 %) than in the pubertal (28 %) and post-pubertal (25 %) children [47].

In a study of children in Argentina, 113 patients received ATDs for prolonged periods [48]. After 10 years of treatment, 33 % of the patients treated with ATDs went into remission [48].

An important prospective study performed in France reported that drug therapy for 8 years or longer was associated with about 50 % remission rates in children [8]. One hundred fifty-four children with GD diagnosed between 1997 and 2002 were examined following treatment with carbimazole. The estimated rates of remission were 20, 37, 45 and 49 %, after 4, 6, 8 and 10 years of therapy, respectively [8]. However, if one includes all the children in the study, the overall remission rate was about 30 %.

More recently, in a larger retrospective analysis from Japan of 1138 children, 723 were continued on long-term ATD treatment, 271 underwent surgery or RAI and 144 dropped out. Of the 639 patients who continued long-term ATD treatment, 46.2 % achieved remission after 8 years of treatment, and 34.2 % relapsed. The prevalence of adverse events associated with MMI and PTU were 21.4 and 18.8 %, respectively [12]. Considering all of the patients enrolled, including those who had definitive therapy or discontinued medication due to adverse events, the overall remission rate was about 30 %.

Other studies of long-term remission rates of pediatric GD treated with ATDs for up to 10 years have been recently published. Remission rates were very low (<20 %), even with long-term therapy in cohorts from Germany (65 patients) [11] and Denmark (237 patients) [10].

Collectively, these data show that the majority of children with GD treated with ATDs, even for prolonged periods of time, do not go into remission. And in those children, who tolerate prolonged ATD therapy for 8 years or more, remission rates will be 40 % at best. For those children with unfavorable risk factors for spontaneous remission at treatment onset, it is reasonable to treat children for up to 2 years with MMI and see whether spontaneous remission has occurred. At that point, if there is no remission, it is appropriate to move on to definitive therapy if desired by the family. Alternatively, treatment for longer periods can be considered, as long as side effects to medication do not occur. This approach may be especially useful if the child is considered too young for surgery or radioactive iodine.

For the child with favorable risk factors for remission, if spontaneous remission has not occurred after the 2 years of ATDs, continuation of antithyroid medication for prolonged periods is also acceptable. Parents, though, need to be informed that chance of spontaneous remission will be less than the need for definitive treatment.

Are there risks with long-term ATD therapy?

For individuals who are long-term ATD therapy, it is important to recognize that the risks of MMI and PTU are clearly greater than the risks of replacement doses of levothyroxine [12, 39]. Whereas adverse events to these medications most commonly occur within the first 6 months of treatment, they can occur any time over the course of therapy [12, 39]. Thus, one should never be lured into a false sense of security for child on long-term ATD treatment.

An issue that remains to be determined is whether those children who go into remission following prolonged ATD therapy will have a higher risk of thyroid cancer. GD is associated with a higher rate of thyroid cancer than the normal population [49–51]. Data from the Cooperative Thyrotoxicosis Study Group show that when one compares rates of thyroid cancer and mortality due to thyroid cancer, individuals treated with ATDs have a cancer rate that is tenfold that of individuals treated by radioactive iodine or surgery [52, 53].

Another potential complication of prolonged ATD therapy relates to the risk of ANCA-mediated vasculitis. Although ATDs can be used long term, reports describe the development of anti-neutrophil cytoplasmic antibodies (ANCAs), which are associated with vasculitis and may limit prolonged medical therapy [54–56]. In adults up to 15 % of individuals treated with PTU, develop ANCAs after 2 years of therapy [54, 55]. MMI use is also associated with ANCA-positivity conversion, albeit with a lower incidence than PTU [54, 55].

Because ANCA antibodies can trigger serious vasculitis events, antithyroid medications should be stopped and definitive therapy considered when ANCA antibodies are detected [21]. To test for this potential problem, it is reasonable to perform annual assessment of ANCAs on children on prolonged ATD therapy, i.e., more than 2 years. However, this issue requires additional study.

Another problem with long-term therapy is the penalty of delaying the inevitable. For individuals with clinical characteristics that portend a slim chance of remission, and definitive therapy can be rendered with low risk, one needs to ask how long is it appropriate to delay treatment if remission is not achieved? This consideration is especially important for teenagers before they leave pediatric care and become of childbearing age for several reasons. It is well recognized that the health care of young adults may be less comprehensive and sporadic than that of adolescents [57, 58]. The management of pregnancy is more complicated for an individual on ATDs versus an individual replacement levothyroxine [34, 59].

Issues related to radioactive iodine use in the pediatric population

Radioactive iodine use for thyroid ablation was introduced in the 1940s at the Massachusetts Institute of Technology and Massachusetts General Hospital [18, 60]. Because of a longer half-life, ^{131}I is the favored iodine isotope for treating thyroid cancer and hyperthyroidism. As with surgery, the goal for ^{131}I therapy for GD is to induce hypothyroidism. Radioactive iodine should not be given to cause euthyroidism in children, as this results in partially irradiated residual thyroid tissue that will be associated with a higher risk of thyroid neoplasm than the normal population [52, 61].

It has been suggested that dosages delivering 30,000–40,000 cGy (rad) to the thyroid are necessary to ablate the thyroid gland [62, 63]. But, dosages delivering 10,000–20,000 cGy to the thyroid are more often used and result in partial or complete destruction of the thyroid [4, 64, 65]. Typically, administered thyroid doses of 150 uCi/gm (5.5 MBq/gm) generate radiation doses of 12,000 cGy to the thyroid [66].

Some centers give a fixed administered dosage of 10 or 15 mCi ^{131}I to all children [67], rather than individually calculated administered activation. There are no studies comparing outcomes of fixed doses versus calculated doses in children. In adults, the two different approaches lead to similar outcomes [68, 69]; however, in children, a potential advantage of calculated versus fixed dosing is that it might be possible to use lower dosages of ^{131}I if the administered dose is calculated.

When children are to be treated with ^{131}I, ATDs should be stopped 3–5 days prior to treatment [70] (Table 2). Patients are then placed on beta-blockers until T4 and/or free T4 levels normalize post-therapy. Whereas some clinicians restart ATDs after treatment with^{131}I, this is rarely required in children [4, 67, 70, 71]. Thyroid hormone levels begin to decrease about 7 days after radioiodine therapy in children, and continued ATD use can make it difficult to assess if post-treatment hypothyroidism is the result of ^{131}I or the ATD.

Table 2 Recommendations for the use of ^{131}I

Stop antithyroid drugs 3-5 days before therapy
Begin beta-blocker when antithyroid drugs stop
No need to restart antithyroid drugs after ^{131}I
Check thyroid hormone levels every 30 days after therapy
2–4 months before hypothyroidism ensues
5 % or more in a get a good weekend after a need retreatment
Not effective if gland >80 gm
Avoid in children less than 5 years of age
When used between 5 and 10 years of age, use less than 10 mCi if possible

Side effects of ^{131}I therapy are unusual. Less than 10 % of children will complain of mild tenderness over the thyroid in the first week after ^{131}I therapy [70, 71]. This can be treated with either acetaminophen or non-steroidal, anti-inflammatory agents for 24–48 h [70, 71].

There are rare reports of children with severe hyperthyroidism developing thyroid storm after ^{131}I [72]. In general, these children were severely hyperthyroid when ^{131}I was rendered. Thus, if T4 levels are >20 ug/dl (200 nmol/l) or free T4 levels are >5 ng/dl (60 pmol/l), children should be treated with MMI until T4 and/or free T4 levels normalize before proceeding with ^{131}I therapy [70, 73]. It is important to recognize that most children with GD have been hyperthyroid for months prior to diagnosis; there is no need to rush to ^{131}I therapy.

It usually takes 6–12 weeks after ^{131}I treatment for the patient to become biochemically euthyroid or hypothyroid. Until then, symptoms of hyperthyroidism can be controlled using beta-blockers [74–76]. The use of SSKI or Lugol's solution 1 week after ^{131}I will also quickly attenuate biochemical hyperthyroidism without adversely affecting the outcome of radioiodine therapy [76].

What are outcomes of radioactive iodine in children?

Several studies have reported the details of ^{131}I therapy for childhood GD [15, 77–83]. Children as young as 1 year old have been treated with ^{131}I with excellent results [83, 84]. But, treatment of such young children is not common, nor is now recommended. ^{131}I dosages in children and teenagers have ranged from 100 to 400 uCi/gm of thyroid tissue [4]. Similar to that found in adults [65, 85, 86], responses to ^{131}I therapy are related to gland size and dose. 25–40 % of children treated with 50–100 uCi of ^{131}I per gm of thyroid tissue are hyperthyroid several years after therapy [61]. In children treated with 150–200 uCi of ^{131}I per gm thyroid, hyperthyroidism remains in 5–20, and 60–90 % become hypothyroid [4, 21, 64, 81, 84].

Our group analyzed outcomes of the children treated with radioactive iodine therapy to assess the effectiveness of therapy as related to gland size and dose [70]. Following treatment, when treated with 80–120 uCi of ^{131}I per gm of thyroid tissue, 28 % of children were hyperthyroid, 28 % of children were euthyroid and 42 % of children were hypothyroid. Following treatment with 200–250 uCi per gm of thyroid tissue, 37 % of children were hyperthyroid and 62 % were hypothyroid. Following, treatment with 300–400 uCi per gm of thyroid tissue, 0 % of children were hyperthyroid, euthyroid and 93 % were hypothyroid. Comparing these pediatric data with those from adults [65, 70, 85], thyroid tissue of children

appears to be more sensitive to ^{131}I induced ablation than adults.

As in adults, we find that gland size influences therapy outcomes. In general, higher dosages per gm of thyroid tissue are needed with larger than smaller glands. Yet, with glands larger than 80 gm, ^{131}I efficacy is low and is not recommended.

Can radioactive iodine be used in children with ophthalmopathy?

The development of progression of ophthalmopathy following ^{131}I in adults has been reported [5–7]. However, unlike adults, children rarely develop severe ophthalmopathy and proptosis is mild [4, 21, 34].

Studies show that disease worsens in only a small percentage of children with GD, irrespective of therapy type. Of 87 children treated with ^{131}I for GD at one center, proptosis improved in 90 % of children, did not change in 7.5 % and worsened in 3 % post-therapy [84, 87]. In 45 children who had ophthalmopathy at the onset of treatment at another center, eye disease improved in 73 % and worsened in 2 % after 1 year or more of drug therapy [88]. After subtotal thyroidectomy in 80 children, eye disease was worsened in 9 % [89] and was stable in 75 % after total surgical thyroidectomy [89].

In adults, it has been shown that progression of ophthalmopathy can be prevented by treatment with prednisone for 3 months following ^{131}I therapy [7, 34]. Adjunctive prednisone therapy is not routinely recommended for the majority of children, as most do not have significant eye disease. The prolonged administration of prednisone is also associated with growth failure, weight gain and immune suppression. Nevertheless, prednisone may be useful for the child who has moderate or severe eye disease and will be treated with ^{131}I.

What are the risks of radioactive damage in children treated for GD?

There is no evidence showing adverse effects to offspring of children treated with ^{131}I. Birth defects are not higher in 500 offspring born to about 370 individuals treated with ^{131}I for hyperthyroidism during childhood or adolescence [4]. Additionally, the rates of birth defects are not higher in children treated with 80–700 mCi of ^{131}I for thyroid cancer, which are dosages that are much higher than those used for GD [90].

The thyroid gland is unique in its developmental sensitivity to malignancy after low-level radiation exposure [91–94]. There is an increased risk of thyroid cancer in individuals less than 20 years of age at the time of low-level thyroid irradiation [91–93]. In contrast, individuals who are older than 20 years of age do not exhibit an increased risk of thyroid cancer when exposed to low-level thyroid irradiation [91–94].

The risk of thyroid neoplasms in children is greatest with exposure to low-level external radiation (0.1–25 Gy; ~0.09–30 uCi/gm) [21, 91–95] and not with the higher dosages used to treat GD. At present, we are not aware of any cases of thyroid cancer that developed in pediatric patients treated with >150 uCi of ^{131}I per gm of thyroid tissue for childhood GD that can be attributed to ^{131}I therapy.

Important in considering radioactive iodine use in children is the potential influences of ^{131}I therapy on other cancers, as ^{131}I therapy results in low-level, whole body radiation exposure. Several studies in adults have examined potential risks of ^{131}I therapy for GD on cancers. These studies have generally not revealed increased mortality or increased rates of cancer following ^{131}I for GD [53, 96–101].

In comparison with studies in adults, few studies have focused on outcomes of ^{131}I therapy for childhood GD. The most extensive study of pediatric patients involved 36 year outcomes of 116 patients who were less than 20-years old when treated with ^{131}I therapy for GD [102]. There was no evidence for increase cancer risk in this population. Yet, this sample size is small.

The total-body radiation dose after ^{131}I varies with age, and the same absolute dose of ^{131}I will result in more radiation exposure in a young child than in an adolescent or adult [103, 104]. Currently, we do not have dosimetry data on ^{131}I use in pediatric patients with GD to assess total-body exposure in pediatric patients. Based on phantom modeling, it is estimated that at 0, 1, 5, 10, 15 years and adulthood, respective total-body radiation doses will be 11.1, 4.6, 2.4 1.45, 0.90 and 0.85 rem (0.01 Sv) per mCi of ^{131}I administered [103, 104]. Based on the Biological Effects of Ionizing Radiation Committee V (BEIR VII) analysis of low-level, acute exposure to radiation [26], theoretical lifetime attributable risk of cancer mortality and all cancer incidences can be projected. Based on these theoretical calculations, we feel that it is prudent to avoid radioactive iodine therapy in children under 5 years of age and to avoid >10 mCi in patients less than 10 years old. Yet, these recommendations are based on theoretical projections and not on hard data.

We recognize that there may be circumstances when ^{131}I therapy is necessary for young children. The need for ^{131}I in a young child may occur when the child develops a toxic reaction to an ATD, proper surgical expertise is not accessible, or the child is not a suitable surgical candidate. In these circumstances, the lowest dosage possible should be employed.

Surgery for pediatric GD

Surgery is an effective form of therapy for GD if it can be performed by an expert surgeon and in some settings it is preferable to radioactive iodine. When surgery is performed, near-total or total thyroidectomy is indicated, as subtotal thyroidectomy is associated with a higher relapse rate [89]. Hypothyroidism is nearly universal in children and adults who undergo total thyroidectomy [89, 105–107]. In comparison, after subtotal thyroidectomy, hyperthyroidism recurs in 10–15 % of patients [89, 105, 106].

Surgery is preferred in children younger than 5 years when definitive therapy is needed and can be performed by a skilled thyroid surgeon. In individuals who have large thyroid glands (>80 gm), the response to ^{131}I is poor [65, 86]. Thus, surgery is also recommended for these patients.

In preparation for surgery, the patient should be rendered euthyroid. Typically, this is done by continuing MMI until T4 levels normalize. A week before surgery, iodine drops are started (1–3 drops, t.i.d.), which inhibits thyroid hormone production and causes the gland to become firm and less vascular.

Postoperatively, younger pediatric patients are at a higher risk of transient hypoparathyroidism than adolescents or adults [108]. To mitigate postoperative hypocalcemia, we treat children with 0.5 mcg of calcitriol, twice a day, for 3 days prior to surgery. Postoperatively, the calcitriol is weaned over 15 days (0.5 mcg bid × 5 days; 0.5 mcg q.d. × 5 days; 0.5 mcg q.o.d × 5 days) [109]. Using this approach, only 5 % of patients require postoperative calcium infusions versus 40 % of patients without preoperative treatment [109].

Acute complications that follow thyroidectomy include hemorrhage, hypocalcaemia and recurrent laryngeal nerve paresis [108, 110–113]. In children, rates from 0 to 6 years were 22 %, from 7 to 12 years, 11 %; and from 13 to 17 years, 11 % [108]. These rates are higher than those observed in adults.

Who should operate on children with GD?

Complication rates are related to the expertise of surgeon. When performed by pediatric surgeons, the complication rate for total thyroidectomy is approximately 15 % [108]. In comparison, the complication rate in children for high-volume thyroid surgeons (>30 thyroidectomies/year) is approximately 4 % [108].

Considering these data, if local pediatric thyroid surgery expertise is unavailable, referral of a child with GD to a high-volume, thyroid surgery center with pediatric experience should be considered [114, 115]. Very low complication rates for children undergoing the thyroidectomies for GD have been reported with this type of multidisciplinary model [109, 114].

Conclusions

Several aspects of the treatment of Graves' disease remain controversial; however, based on what we know about both the risks of different treatments and the pathogenesis of GD, we can be discriminating in our approach to therapy (Figs. 1, 2). Doing such, it is possible to reduce risks of treatment and personalize the treatment approach. Therapy decision making should be guided by the patient's clinical condition, considering risk factors that portend the likelihood of remission or not.

For those individuals who have favorable factors for remission (normal TSI levels, moderately elevated thyroid hormone levels, normal size thyroid gland, pubertal), it is important to recognize that the chance of remission will be about 40 % at best after 8 years or more of ATDs. These patients constitute the minority of children with GD. MMI

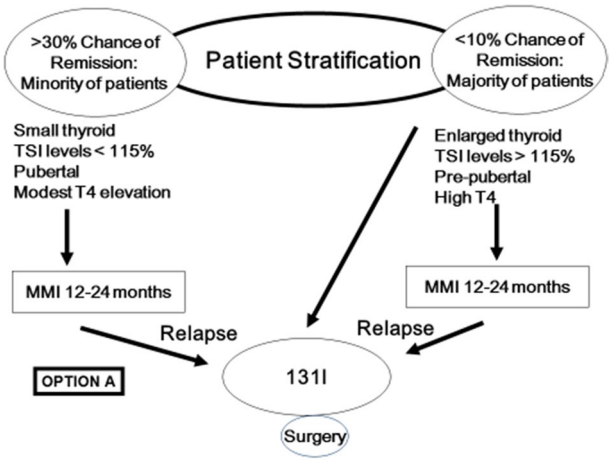

Fig. 1 Option A for treatment of pediatric Graves' disease

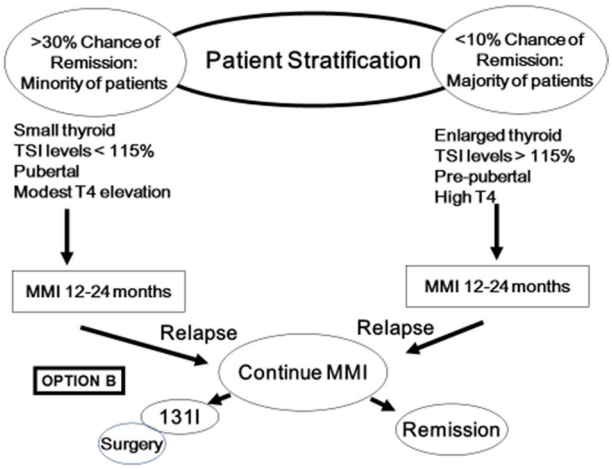

Fig. 2 Option B for treatment of pediatric Graves' disease

can be used in this group of children with long-term hope of achieving spontaneous remission. If remission does not occur, and the family desires definitive therapy in the midst of long-term drug therapy, surgery or radioactive iodine should be considered. This consideration is especially important for teenagers before they leave pediatric care and become of childbearing age, as the risks of definitive therapy are very low in teenagers.

For those individuals, with risk factors indicating a low chance of spontaneous remission at diagnosis (elevated TSI levels, significantly elevated thyroid hormone levels, thyromegaly and younger age), all treatment options may be initially considered, including MMI. However, definitive therapy in the form of either radioactive iodine or surgery will generally be needed for this cohort. Thus, after about 1–2 years of ATDs, if not in remission, one can consider definitive therapy for this cohort. Considering the potential risks of radioactive iodine or surgery in young children, if toxic reactions to each of these are not occurring in this group of children, it is reasonable to continue medication for extended periods until the patient is viewed old enough for definitive therapy. Fortunately, only 10 % of the pediatric population with GD presents younger than 10 years of age.

When MMI is used, one should consider lower rather than higher doses. It is essential that the patient and family warned of potential side effects and to discontinue medication if any adverse reactions develop. Prior to biochemical control of the hyperthyroid state, symptomatic relief can be achieved through the use of beta-blockers, avoiding the perceived need for higher MMI doses.

When radioactive iodine is used, the dosage administered should begin with the goal of ablating thyroid tissue. Because of the potential risks of full body radiation to young children, it is recommended that this be avoided children less than 5 years of age and used conservatively in children less than 10 years of age. If there is a risk to radioactive iodine use, available data in children and adults show that this risk is very low.

Surgery for GD can be associated with a significant risk of complications in the pediatric population. As such, the decision to operate on children should not be made lightly, and surgery should be performed by expert, high-volume thyroid surgeons.

Lastly, it is important to consider that whatever form of treatment is selected that selection of the approach be done so considering and respecting the viewpoints of the child and family.

Acknowledgments This study was supported in part by NIH grant 7R01FD003707.

Compliance with ethical standards

Conflict of interest None.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent.

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