Scottish Paediatric Endocrine Group National Managed Clinical Network

Medical Management of Children with Thyrotoxicosis

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Approved by the SPEG Guidelines Group
Version 2.0
Current Issue Date: 21/01/2021
To be reviewed: 21/01/2024

NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Contents

Purpose of Guideline

Management of children with thyrotoxicosis

Who should use this document

- Paediatricians
- Paediatric Endocrinologists

To whom this document applies

Children and young people under 16 years of age who have been diagnosed with thyrotoxicosis.

Review group

SPEG MCN guidelines group

Acknowledgement

We gratefully acknowledge Dr Tim Cheetham, Royal Victoria Infirmary
Newcastle upon Tyne for much of this guideline which is based on his protocol for the BSPED RCT of childhood thyrotoxicosis treatment.

Summary

Diagnosis
Based on clinical findings and suppressed TSH, raised thyroid hormones.

Investigations
First Line; TSH, free T4, total T3 (or free t3).
Second line investigations optional, but preferred; TRAb, USS thyroid, Isotope scan thyroid.

Treatment
First line therapy – Drug treatment.
Usually Start with Carbimazole 0.75mg/kg/day.
2 variations in drug treatment; 'block and replace' or titration. Continue for 36 months. Stop then reassess.
Add Propranolol initially if significant autonomic symptoms/signs.

Second line (treatment failure or relapse after 36 months): – Radioiodine therapy or surgery requiring referral to regional centre

Eye disease– refer to ophthalmologist.

Introduction

Thyrotoxicosis is a relatively uncommon disorder in childhood and adolescence. The BPSU survey found an incidence of 0.94 per 100,000 <15yr olds[1]. Most patients with thyrotoxicosis have Graves' disease (84% in the BPSU study) which develops because of thyrotropin (TSH) receptor stimulation by auto antibodies. Patients with Hashimoto's thyroiditis can also be thyrotoxic in the early phase of the disease (12 % of cases in BPSU study). Other causes of thyrotoxicosis are much rarer.

In a child with typical features of thyrotoxicosis (see tables 1,2), the diagnosis is confirmed with a suppressed TSH and raised thyroid hormone levels (either T4 or T3 or both)

Children and adolescents presenting with autoimmune thyrotoxicosis in the UK and throughout Europe are usually treated with antithyroid drugs from diagnosis for 1 - 4 years.[1,2] Treatment is then stopped and patients who relapse return to anti-thyroid drugs or are offered more definitive treatment with surgery or radioiodine. This practice differs from common practice in the USA where there are strong proponents of early use of radioiodine therapy.[4] Other centres may also promote the early use of thyroid surgery as a definitive treatment.

None of these therapies are ideal and each have their own advantages and disadvantages. Particular considerations when managing young people include:

- The high relapse rates following a course of anti-thyroid drug therapy,[5,6]
- Concerns about the morbidity associated with thyroidectomy and
- Concerns about the long term safety of radioiodine.

Patient details to be recorded at diagnosis

- History
- Physical symptoms, Duration of symptoms,
- Psychiatric Symptoms,
- School performance
- Other symptoms of autoimmune disease – vitiligo, coeliac etc.
- Family History of thyroid disease, diabetes, other autoimmune diseases

Table 1. Prevalence of symptoms reported in BPSU survey (110 cases)

	total	Graves' disease	Other cause of thyrotoxicosis
Weight Loss	63.64%	67.40%	44.44%
Fatigue / Tiredness / Lethargy	53.64%	56.50%	38.89%
Change in behaviour	50.00%	53.30%	33.33%
Heat Intolerance	47.27%	50.00%	33.33%
Nervousness /Anxiety	47.27%	50.00%	33.33%
Increased Appetite	47.27%	50.00%	33.33%
Palpitations	30.91%	35.90%	5.56%
Profuse Sweating	26.36%	27.20%	22.22%
Deteriorating school performance	22.73%	25.00%	11.11%
Headache	21.82%	22.80%	16.67%
Diarrhoea	16.36%	16.30%	16.67%
Asymptomatic (e.g. picked up on screening,)	9.09%	8.70%	11.11%
Pain in thyroid gland	3.64%	3.30%	5.56%
Weight Gain	1.82%	2.20%	0.00%

Examination

Record the following findings:

Initial:

- Weight, Height, Growth velocity (if previous Ht available),
- Parents Height if possible
- Cardiovascular assessment including BP, pulse
- Goitre exam, presence of bruit,
- Thyroid volume assessed clinically (consider measuring length of lobes with tape measure)
- Tremor, Hyperkinesia
- Eye exam
  - Elicit lid lag
  - state if proptosis or not
  - Range of eye movements
- Pubertal Assessment,
- Skin

Subsequent examinations during follow up:

- Weight
- Height
- Growth velocity
- Blood Pressure
- Pulse
- Goitre examination
- Eye exam
- Tremor

Table 2. Prevalence of physical signs reported in BPSU survey (of 110 cases):

Signs			
	total	Graves' disease	Other cause of thyrotoxicosis
Goitre	78.18%	82.60%	55.56%
Tremor	58.18%	60.90%	44.44%
Lid retraction (Staring Eyes)	31.82%	37.00%	5.56%
Exopthalmos / Proptosis (forward displacement or bulging of the eye)	29.09%	32.60%	11.11%
Thyroid Bruit	25.45%	29.30%	5.56%
Heart Murmur	7.27%	6.50%	11.11%
Diplopia	1.82%	2.20%	0.00%
Myxoedema	0.91%	1.10%	0.00%
Evidence of life threatening 'thyroid storm' (hyperthermia tachycardia, GI dysfunction, CNS Dysfunction)	0.00%	0.00%	0.00%

Investigations

Bloods

- **Thyroid function** - TSH, free T4 and Total T3, (or free T3, depending on lab)

Initially performed to confirm Thyrotoxicosis.

Expect suppressed TSH and either or both of raised fT4 or Total T3 (some children with thyrotoxicosis have raised T3 but normal T4).

- **Antibodies –** *To confirm Autoimmune thyrotoxicosis and distinguish Graves' from Hashimotos*
- **TSH receptor antibodies (TRAb)** – Presence suggests Graves' Disease,
- **Thyroid Peroxidase antibodies (TPO)** - can be present in both Graves' and Hashimoto's disease.
  Children with persistently high levels of TSH receptor antibodies after treatment with antithyroid medications are more likely to relapse when treatment is discontinued.

Secondary investigations (if available or if diagnosis in doubt)

- **Ultrasound of thyroid** – diffusely enlarged thyroid in Graves, focal enlargement in nodule, Assessment of thyroid volume by ultrasound
- **Technitium (Tc^{99m}) or iodine (^{123}I) uptake scan** – diffusely enlarged in Graves, focal uptake in nodule, diminished uptake in thyroiditis.

Other Investigations of possible or research merit

- **Bone age** – may be advanced
- **DEXA** – reduced bone density

Treatment

Treatment of the child newly diagnosed with Graves' disease is usually medical. In Scotland surgery and radioiodine treatment are also available but are currently reserved as second line treatment. Recently, more evidence of the safety of radioiodine has become available so practice may change in the future[4]. Serious complications of the antithyroid drugs (ATDs) have been reported, particularly agranulocytosis and most often in the first 3 months of therapy but it is not clear how frequently these occur in children.[11, 12]

Treatment with antithyroid drugs

There are two options when treating patients with anti-thyroid drugs. [8, 9]

1. '**Block and replace' (combined) therapy** - where thyroid hormone production is prevented by anti-thyroid drugs and thyroxine is then added in a replacement dose;
2. '**Dose titration' (adaptive) therapy** - where the dose of anti-thyroid drug is adjusted so that hormone production is normalised.

Both strategies are used by adult endocrinologists but it is unclear which of these approaches is the most appropriate in the young person.

Potential advantages of 'block and replace':

- Improved stability with fewer episodes of hyper or hypothyroidism.
- A reduced number of venepunctures and visits to hospital. [8]
- Improved remission rates following a larger anti-thyroid drug dose. [9]

Potential advantages of dose titration:

- Fewer side effects with a lower anti-thyroid drug dose[9,14]
- Improved compliance on one rather than two medications.

It is also possible to partially block thyroid gland function and add thyroxine in a relatively low dose but this guideline will not address this.

The following guide to medical treatment is based on the protocol for the trial carried out by the BSPED to compare dose titration and block and replace.[7]

Treatment Option 1

Block and replace with Carbimazole and thyroxine

'Block and replace' regimen for 36 months.

Carbimazole is commenced in a **total daily dose of 0.75 mg/kg/day**,(5mg and 20mg tablets). Initial Dose should not exceed 40mg per day. The intention is to completely prevent endogenous thyroxine production. Thyroxine is then added in a replacement dose as the patient becomes euthyroid and then hypothyroid.

- If thyroxine values remain elevated (> 2SD, i.e. outside the lab ref range) at 2 months into treatment or beyond with a suppressed TSH then consider increasing the dose to 1 mg/kg. However, it is unlikely that a child will require more than 40mg daily of Carbimazole, so consider compliance issues if larger doses appear necessary.
- When Free thyroid hormone levels are <15 pmol/l, start thyroxine in a low replacement dose ~ 75 micrograms / m^2.
- If the TSH is suppressed and the free thyroxine is low or in the bottom part of the normal range in the initial phase of treatment (the first 4 months) then thyroxine should still be commenced. (A delay in the rise of TSH after treatment has commenced is common).
- The treatment regimen may not require adjustment if the free thyroxine is relatively high but the TSH is normal.
- If compliance is not a concern and if the dose of thyroxine is not greater than 75micrograms/m^2 then a suppressed TSH beyond the first 4 months of therapy should be managed by increasing the dose of carbimazole in the first instance.
- If the patient becomes thyrotoxic with a suppressed TSH when the biochemistry has been normal at an earlier stage of therapy – check compliance and consider increasing the dose of carbimazole by 5 mg/day. It is unlikely that a child will require more than 40mg daily of Carbimazole, so consider compliance issues if larger doses appear necessary.
- If the patient subsequently develops a high TSH then increase the dose of thyroxine up to 100 micrograms/m^2/day or by 12.5 to 25 microgram increments (12.5 micrograms under 30 kg, 25 micrograms for those over 30kg).

Treatment Option 2

Dose titration with carbimazole

Dose titration for 36 months with carbimazole alone.

Carbimazole is commenced in a **total daily dose of 0.75 mg/kg/day** until the child is euthyroid (the initial dose should not exceed 40mg per day).
The dose is then reduced to 0.25 mg/kg/day with the intention of maintaining a euthyroid state.

The primary objective of treatment is to maintain free T_4 concentrations in the normal laboratory range with a TSH that is also within the normal laboratory range (neither elevated nor suppressed):

- The dose of carbimazole will be adjusted up or down depending on the thyroid function. It is unlikely that a child will require more than 40mg daily of Carbimazole, so consider compliance issues if larger doses appear necessary.
- If the patient is hypothyroid then the carbimazole dose will be reduced by 5mg/day for those patients under 30 kg and 10 mg for those over 30kg.
- If the patient is hyperthyroid then it will be increased by 5mg for those patients under 30 kg and 10 mg for those over 30kg.
- Be primarily guided by the thyroid hormone value (not the TSH) in the first 4 months after diagnosis.
- Be guided by both the TSH and free T4 thereafter; if the TSH is suppressed in the presence of normal free T4 values then consider reducing the dose of carbimazole as detailed above.
- The treatment regimen may not, therefore, need to be adjusted if the TSH is suppressed and the free thyroxine is normal in the initial phase of treatment (the first 4 months).
- The treatment regimen may not need to be adjusted if the free thyroxine is relatively high but the TSH is normal (analogous to the congenital hypothyroid patient who may have a normal TSH but a relatively high free T4 when on T4 replacement).

Propylthiouracil

Most paediatricians in the UK commence thyrotoxic children on **carbimazole** rather than **propylthiouracil** although either drug can be taken once a day and they have similar side effects. The guidelines detailed here can be used in the knowledge that 1mg of carbimazole is *approximately* equivalent to 10 mg of propylthiouracil.

Propranolol

- Propranolol or other beta-blockers can be used to give relief from symptoms such as anxiety, tremor and palpitations in the first few weeks of treatment.
- Propranolol can be given orally at a dose of 250–750 µg/kg/dose three times per day.
- It can be weaned and stopped as the patient becomes euthyroid.

Side effects of carbimazole and propylthiouracil (Thionamides)

- Minor side effects such as rashes, nausea, and headaches occur in 2–15% of patients and usually develop during the first weeks of therapy.
- Agranulocytosis is reported to occur in 0.1-0.5% of patients on either carbimazole or propylthiouracil in equal numbers. It most often occurs in the first 3 months after starting treatment, but occasionally a long time afterwards. It also occurs suddenly, so routine monitoring of full blood count is of little use.

> ***CSM Warning (neutropenia and agranulocytosis)***
>
> Doctors are reminded of the importance of recognising bone marrow suppression induced by carbimazole and the need to stop treatment promptly.
>
> 1. Patient should be asked to report symptoms and signs suggestive of infection, especially sore throat.
> 2. A white blood cell count should be performed if there is any clinical evidence of infection.
> 3. Carbimazole or Propylthiouracil should be stopped promptly if there is clinical or laboratory evidence of neutropenia.

Hepatitis can be severe and fulminant. It is more common with PTU and families should be warned to stop therapy in the event of jaundice, dark urine, or pale stools.

Alternatives to Carbimazole and Propylthiouracil

Iodide blocks thyroid hormone synthesis and release and can be administered in addition to ß blockade. Its action tends to diminish over time so it cannot be used in the long term. Lithium also has antithyroid properties by blocking thyroxine release and has been used occasionally in adults before surgery and radioiodine treatment.

Treatment Failure and Second Line Treatment Options.

Radioiodine therapy and Surgery are definitive treatment options for thyrotoxicosis. They will ultimately render the child permanently euthyroid, or hypothyroid (requiring long-term thyroxine replacement). Although drug based treatments are currently the favoured

treatment option outlined here, there are several reasons that a definitive treatment option may be sought:

- Treatment failure – for compliance reasons, medical treatment may fail to allow the child to reach a euthyroid state for any reasonable time.
- 'Relapse' – After 36 months a trial off drug therapy may result in a recurrence of thyrotoxicosis. The patient may choose to continue drug therapy in the long term or may wish definitive treatment.
- Patient choice

Patient choice

As outlined above, there are pros and cons of each treatment option in thyrotoxicosis. Before embarking on a particular treatment plan, the child and their parents should be equipped to make an informed choice by meeting to discuss the options with their paediatric endocrinologist, the radiologist and the surgeon. Referrals for this may need to be made across NHS trusts depending preferences and availability of these services.

Radioiodine Therapy

The aim of radioiodine therapy is to ablate the thyroid and render the patient hypothyroid. Antithyroid medication should be stopped 3–7 days prior to RI therapy and be recommenced, if necessary, one week afterwards. It should be restarted earlier in the patient thought to be at risk of a thyroid storm, although this may also compromise the efficacy of RI therapy. Titrating the RI dose according to gland size requires a tracer dose of ^{131}I, and recent reports have used a predetermined amount between 300 and 550 MBq during adolescence. Patients should be reviewed within the first few days after RI therapy because of the small possibility of a thyroid "crisis", and then every six weeks so that thyroxine replacement can be initiated before the patient becomes profoundly hypothyroid. Some patients will require a second dose of RI (more likely if lower doses are used). Children and adolescents receiving RI in an average dose of 14.7 mCi (~540 MBq), hypothyroidism developed between 40 and 90 days in 75% of patients.[14]

Surgery

Subtotal thyroidectomy has the potential to render the patient euthyroid off therapy although the likelihood of recurrence or of hypothyroidism has resulted in many surgeons recommending total thyroidectomy.

Eye Disease

Around one third of children with thyrotoxicosis will have significant eye disease. This ranges from minimal lid lag through proptosis to ophthalmoplegia. It is recommended that an opthalmological opinion be sought soon after the diagnosis in these cases. Some children may develop eye signs after diagnosis and treatment has been established. There is a well established link between severity of eye disease and active smoking. Children who smoke should be informed of this[14,15]. Steroid prophylaxis is required prior to RI therapy, if there are concerns about eye disease.(Kahaly et al).

Other Causes of Thyrotoxicosis

'Hashitoxicosis' may be indistinguishable initially from Graves disease biochemically and should be treated is the same way. A Technetium (Tc^{99m}) or iodine (^{123}I) uptake scan will show reduced uptake rather than increased uptake. TPO and thyroglobulin antibodies may be present in both diseases, but a raised TRAb titre is indicative of Graves' disease.

'Hot thyroid nodules' are practically always benign (non-cancerous). Diagnosis is by ultrasound and isotope scan. Treatment options are primarily surgical (partial lobectomy) or Radioiodine.

Thyroid storm (thyrotoxic crisis)[13]

This presents with fever, sweating, tachycardia, hypertension leading to high output cardiac failure. Patients may also have seizures.

Thyroid storm requires emergency In-patient Care by an experienced endocrinologist with:

- intravenous administration of fluids.
- antithyroid medication – large doses of propylthiouracil +/- iodide.
- propranolol to minimise the adrenergic effects
- hydrocortisone (high risk of adrenal insufficiency).
- Also treat the precipitating factor of the crisis such as infection.

Suggested follow up and investigations

Based on BSPED trial protocol[7]

	Exam[n]	Check for possible side effects incl. sore throats	Thyroid function	Antibodies	Bone age	Thyroid U/S	Other
Diagnosis and Visit 1	*		*	*	*		* Isotope scan
Visit 2: 4 weeks	*	*	*				
Visit 3: 6 weeks	*	*	*				
Visit 4: 8 weeks	*	*	*				
Visit 5: 12 weeks	*	*	*				
Visit 6: 6 months	*	*	*				
Visit 7: 9 months	*	*	*				
Visit 8: 12 months	*	*	*				
Visit 9: 15 months	*	*	*				
Visit 10:18 months	*	*	*				
Visit 11: 21 months	*	*	*				
Visit 12: 24 months	*	*	*				
Visit 13: 27 months	*	*	*				
Visit 14: 30 months	*	*	*				
Visit 15: 33 months	*	*	*				
Visit 16: 36 months	*	*	*	*	*	*	
Visit 17: 48 months	*	*	*	*	*	*	

Useful reading

2018 European thyroid ass

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