Hyperthyroidism in children

Dr. Shahab Noorian Ped. Endocrinologist
Assistant professor of Alborz University
What is hyperthyroidism?

• **Hyperthyroidism** (overactive thyroid) is a condition in which the thyroid gland makes too much thyroid hormone.

• The over-secretion of thyroid hormone leads to over-activity of the body's metabolism

• causing sudden weight loss, a rapid or irregular heartbeat, sweating and nervousness or irritability.
Thyrotoxicosis, however, refers to the clinical effects of unbound thyroid hormones, whether or not the thyroid gland is the primary source.
Causes of Hyperthyroidism

- The vast majority of hyperthyroidism cases are caused by Graves’ disease (autoimmune hyperthyroidism).

- Hyperthyroidism can also be caused by an autonomous hot nodule

- or by a non-immune inflammation, such as a viral or bacterial infection
Some Causes of Thyrotoxicosis

- **Graves' Disease**
- **Toxic multinodular goitre**
- **Toxic adenoma**
- **Thyroiditis**
- Other less common causes of thyrotoxicosis, accounting for the remaining are:
  - Factitious Thyrotoxicosis - patients taking too much thyroid hormone
  - Drug-induced Thyrotoxicosis (e.g. Iodine, Thyroid hormone or Amiodarone - see below)
  - Neonatal Thyrotoxicosis
  - Ectopic Hyperthyroidism - from a TSH-secreting tumour
  - **Struma ovari**
How should clinically discovered hyperthyroidism?

- If the child is suddenly losing weight
- has become irritable or depressed
- and is having trouble concentrating in school,
- it may be time to call the doctor
Graves' disease is by far the most common cause of hyperthyroidism in children and adolescents.

Overall, the prevalence of Graves' hyperthyroidism in children is approximately 0.02 percent (1:5000), mostly in the 11- to 15-year age group.

In a report of 143 children with Graves' disease, 38 percent were prepubertal at diagnosis.

Girls are affected more commonly than boys, at a ratio of about 5:1. The ratio is considerably lower among younger children, suggesting that estrogen secretion in some way affects the occurrence of Graves' disease.

What are the symptoms of hyperthyroidism?

- Anxiousness, irritability and/or nervousness
- **Poor, restless sleep**
- Increased activity/fidgetiness, hyperactivity, restlessness
- **Fatigue**
- Increased appetite with or without weight loss
- Increased number of bowel movements per day
- **Heat intolerance** (always feeling warm)
- Decreased or poor school performance; difficulty concentrating that may be diagnosed as "late-onset" attention deficit disorder
- Feeling of a “**lump**” in the throat
All patients with known or suspected hyperthyroidism should undergo physical examination, including:

- measurement of pulse rate
- blood pressure,
- respiratory rate
- and body weight.
- thyroid size
- presence or absence of thyroid tenderness,
- symmetry, and nodularity;
- pulmonary, cardiac, and neuromuscular function
- presence or absence of peripheral edema
- eye signs, or pretibial myxedema should be assessed.

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How is hyperthyroidism diagnosed?

In addition to the signs and symptoms of Graves' disease, the diagnosis of hyperthyroidism is confirmed:

- by blood tests and, on occasion
- by thyroid ultrasound
- or nuclear medicine uptake and scan.
- A thyroid uptake and scan helps determine how well the thyroid tissues absorb iodine.

Hyperthyroidism Management Guidelines, *Endocr Pract.* 2011;17(No. 3)
In overt hyperthyroidism, usually both serum free T4 and T3 estimates are elevated, and serum TSH is undetectable; however, in milder hyperthyroidism, serum T4 and free T4 estimates can be normal, only serum T3 may be elevated, and serum TSH will be <0.01 mU/L (or undetectable).

These laboratory findings have been called “T3-toxicosis” and may represent the earliest stages of disease or that caused by an autonomously functioning thyroid nodule.

In "early" Graves’ disease the T3 may be elevated before the T4.

The presence of thyroid receptor antibodies (TRAb), help to confirm the diagnosis.

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Imaging studies may be used to more completely define the hyperthyroidism.

The classic findings on thyroid ultrasound include an enlarged thyroid gland with increased blood flow throughout the gland.

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A radioactive iodine uptake should be performed when:
- the clinical presentation of thyrotoxicosis is not diagnostic of GD
- a thyroid scan should be added in the presence of thyroid nodularity.

In a patient with a
- symmetrically enlarged thyroid
- recent onset of opthalmopathy,
and moderate to severe hyperthyroidism the diagnosis of GD is sufficiently likely that further evaluation of hyperthyroidism causation is unnecessary.

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It is usually:
- elevated in patients with GD
- and normal or high in toxic nodular goiter, unless there has been a recent exposure to iodine (e.g., radiocontrast).
- The pattern of RAIU in GD is diffuse unless there are coexistent nodules or fibrosis.
- The pattern of uptake in a patient with a single TA generally shows focal uptake in the adenoma with suppressed uptake in the surrounding and contralateral thyroid tissue.

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How should GD be managed in children and adolescents?

- Children with GD could be treated with:
  - methimazole
  - 131I therapy
  - or thyroidectomy.

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Most children and adolescents will be started on anti-thyroid medication at the time of diagnosis.

For patients with severe symptoms, including elevated heart rate, palpitations, and anxiousness, a medicine called a "beta-blocker" will be added to help decrease symptoms while the anti-thyroid medications take effect.

Hyperthyroidism Management Guidelines, *Endocr Pract.* 2011;17(No. 3)
Prior to initiating **antithyroid drug** therapy, we suggest that pediatric patients have, as a baseline,
- complete **blood cell** count, including white blood cell count with differential,
- and a liver profile including **bilirubin**, **transaminases**, and **alkaline phosphatase**.

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In addition, a baseline absolute neutrophil count <500/mm³ or liver transaminase enzyme levels elevated more than fivefold the upper limit of normal are contraindications to initiating antithyroid drug therapy.
Because some children will go into remission:
- MMI therapy for 1–2 years is still considered first-line treatment for most children.

However, the majority of pediatric patients with GD will eventually require either radioactive iodine or surgery.

When ATDs are used in children, only MMI should be used, except in exceptional circumstances.

If clinical characteristics suggest a low chance of remission at initial presentation, 131I, or surgery may be considered initially.
Other treatment

- If remission is not achieved after a course of therapy with ATDs, 131I or surgery should be considered.

Alternatively, MMI therapy may be continued until the child is considered old enough for surgery or radioactive iodine.

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If antithyroid drugs are chosen as initial management of GD in children, how should the therapy be managed?

- MMI comes in 5 or 10 mg tablets and can be given once daily, even in patients with severe hyperthyroidism.
- Although many practitioners give MMI in divided doses.
- The MMI dose typically used is 0.2–0.5 mg/kg daily, with a range from 0.1–1.0 mg/kg daily (1).

One approach is to prescribe the following whole tablet or quarter to half-tablet doses:
- infants, 1.25 mg/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.
- With severe clinical or biochemical hyperthyroidism, doses that are 50%–100% higher than the above can be used (2).


(2) Hyperthyroidism Management Guidelines, Endocr Pract. 2011;17(No. 3)
When thyroid hormone levels normalize

- MMI doses can be **reduced by 50% or more to** maintain a euthyroid state (1).
- Alternatively, some physicians elect not to reduce the MMI dose and add levothyroxine to make the patient euthyroid, a practice referred to as **“block and replace”**.
- However, because meta-analyses suggest a higher prevalence of adverse events using block-and-replace regimens than dose titration and there may be dose-related complications associated with MMI (2), we suggest that this practice in general **be avoided**.

Persistent hyperthyroidism beyond 3–4 months suggests that the dose needs to be increased although compliance should also be reviewed.

Serum TSH levels can remain suppressed for months in patients who have been thyrotoxic for a long time.

G Birrell, T Cheetham, Juvenile thyrotoxicosis; can we do better? Arch Dis Child 2004;89:745–750. doi: 10.1136/adc.2003.035980
Cautions for Pediatric patients

**Stopping** the medication immediately and informing their physician if they develop:

- pruritic rash
- jaundice
- acolic stools or dark urine
- arthralgias
- abdominal pain, **nausea, fatigue, fever,**
- or pharyngitis

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physician alertness

Antithyroid medication should be stopped immediately, and **white blood counts** measured in children who develop
- fever,
- arthralgias,
- mouth sores,
- pharyngitis,
- malaise.

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After initiation of MMI therapy, thyroid function tests (estimated free T4, total T3, TSH) are obtained **monthly at first**, and then every 2–4 months. Depending on the severity of hyperthyroidism, it can take several months for elevated thyroid hormone levels to fall into the normal range on ATDs.
PTU is associated with an unacceptable risk of **hepatotoxicity** in children, with a risk of liver failure of 1 in 2000–4000 children taking the medication*. PTU can cause **fulminant hepatic necrosis** that may be fatal; liver transplantation has been necessary in some patients taking PTU. It is for this reason that the FDA recently issued a **safety alert** regarding the use of PTU, noting that 32 (22 adult and 10 pediatric) cases of **serious liver injury** have been associated with PTU use.

Because PTU-induced liver injury is of rapid onset and can be rapidly progressive, however, when neither prompt surgery nor 131I therapy are options, and ATD therapy is necessary in a patient who has developed a minor toxic reaction to MMI, a short course of PTU use can be considered.

*Eunice Kennedy Shriver National Institute of Child Health and Human Development. Hepatic Toxicity Following Treatment for Pediatric Graves' Disease Meeting on October 28, 2008.*
PTU should be stopped immediately

- When propylthiouracil is used in children, the medication should be stopped immediately and liver function and hepatocellular integrity assessed in children who experience:
  - anorexia
  - pruritis
  - rash
  - jaundice
  - light-colored stool
  - or dark urine
  - joint pain
  - right upper quadrant pain
  - or abdominal bloating
  - nausea
  - or malaise

PTU should **not be** used in **pediatric** patients unless the patient is **allergic** to or **intolerant** of methimazole, and no other treatment options are available (1)


(2)Hyperthyroidism Management Guidelines, *Endocr Pract.* 2011;17(No. 3)
PTU should be discontinued if transaminase levels (obtained in symptomatic patients or found incidentally) reach 2–3 times the upper limit of normal and fail to improve within a week with repeat testing.

After discontinuing the drug, liver function tests (i.e., bilirubin, alkaline phosphatase, and transaminases) should be monitored weekly until there is evidence of resolution.

If there is no evidence of resolution, referral to a gastroenterologist or hepatologist is warranted.

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- **MMI** has a better overall safety profile than PTU
- MMI is associated with minor adverse events that may affect up to 20% of children.
- **MMI-related** adverse events include allergic reactions, rashes, myalgias, and arthralgias, as well as hypothyroidism from overtreatment.
- **Side effects** to MMI usually occur within the first 6 months of starting therapy, but adverse events can occur later.
- In children, the risks of cholestasis and hepatocellular injury appear to be much less than that observed in adults.

Agranulocytosis has been reported in about 0.3% of adult patients taking MMI or PTU.

Data on the prevalence of agranulocytosis in children are unavailable, but it is estimated to be very low.

In adults, agranulocytosis is dose dependent with MMI, and rarely occurs at low doses.

When agranulocytosis develops, 95% of the time it occurs in the first 100 days of therapy.

The overall rate of side effects to ATDs (both major and minor) in children has been reported to be 6%–35%.


When we need CBC

- Routine monitoring of white blood counts may occasionally detect early agranulocytosis,
- But it is not recommended because of the rarity of the condition and its sudden onset, which is generally symptomatic.
- It is for this reason that measuring white cell counts during febrile illnesses and at the onset of pharyngitis has become the standard approach to monitoring.

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Management of allergic reactions in children taking methimazole

Persistent minor cutaneous reactions to methimazole therapy in children should be managed by:

- concurrent antihistamine treatment
- or cessation of the medication and changing to therapy with radioactive iodine or surgery.

Hyperthyroidism Management Guidelines, *Endocr Pract.* 2011;17(No. 3)
serious allergic reactions to MMI

In the case of a serious allergic reaction to an antithyroid medication, prescribing the other antithyroid drug is not recommended.

If children develop serious allergic reactions to MMI,

- radioactive iodine or surgery should be considered
- because the risks of PTU are viewed to be greater than the risks of radioactive iodine or surgery. PTU may be considered for short-term therapy in this setting to control hyperthyroidism in preparation for surgery.

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Duration of methimazole therapy in children with GD

- If **methimazole** is chosen as the first-line treatment for GD in children,
- it should be administered **for 1–2 years** and then discontinued,
- or the dose reduced, to assess whether the patient is in remission.

Pediatric patients with GD who **are not** in remission following **1–2 years** of methimazole therapy should be considered for treatment with **radioactive iodine or thyroidectomy**.

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In children, when ATDs are used for 1–2 years, remission rates are generally 20%–30%, remission defined as being euthyroid for 1 year after cessation of therapy.

- Initial response to antithyroid medication, with achievement of euthyroid state within 3 months, suggesting higher likelihood.
- Younger children and those with high initial thyroid hormone levels were also found to be less likely to achieve remission within 2 years in the prospective study (1,2).

(2) Hyperthyroidism Management Guidelines, *Endocr Pract.* 2011;17(No. 3)
who has low remission rate?

- chance of remission after 2 years of ATDs is **low**
  - if the **thyroid gland** is large (more than **2.5** times normal size for age),
  - the child is young (**<12 years**) 
  - not Caucasian
  - serum **TRAb** levels are above normal on therapy,
  - or **FT4** estimates are substantially elevated at diagnosis (**>4 ng/dL**) (1) (2).


(2) Hyperthyroidism Management Guidelines, *Endocr Pract.* 2011;17(No. 3)
As a bridge

- If after stopping MMI after **1 or 2 years**’ remission is not achieved, **131I or surgery** should be considered, depending on the age of the child.
- Alternatively, practitioners can **continue MMI** for extended periods, as long as adverse drug effects do not occur and the hyperthyroid state is controlled.
- This approach can be used **as a bridge** to 131I therapy or surgery at a **later age** if remission does not occur.
- In selected situations **where it might not be** suitable or possible to proceed with **131I or surgery**, **low-dose MMI** can be continued, although the likelihood of remission is not great.

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If radioactive iodine is chosen as treatment for GD in children, how should it be accomplished?

- Children with GD having total T4 levels of >20 ug/dL or free T4 estimates >5 ng/dL who are to receive radioactive iodine therapy be pretreated with methimazole and beta-adrenergic blockade until total T4 and/or free T4 estimates normalize before proceeding with radioactive iodine.

There are rare reports of pediatric patients with severe hyperthyroidism who have developed thyroid storm after receiving 131I (1).

When children receiving MMI are to be treated with 131I:

- the medication is stopped 3–5 days before treatment.
- At that time, patients are placed on beta-blockers, which they continue to take until total T4 and/or free T4 estimate levels normalize following radioactive iodine therapy.

- Although some physicians restart ATDs after treatment with 131I, this practice is seldom required in children.

- Thyroid hormone levels in children begin to fall within the first week following radioactive iodine therapy.

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Radioactive iodine is excreted by saliva, urine, and stool. Significant radioactivity is retained within the thyroid for several days. Patients and families be informed. After 131I therapy, T3, T4, and/or estimated free T4 levels should be obtained every month.

Because TSH levels may remain suppressed for several months after correction of the hyperthyroid state, TSH determinations may not be useful in this setting for assessing hypothyroidism.

Hypothyroidism typically develops by 2–3 months post-treatment (1,2), at which time levothyroxine should be prescribed.

Radioactive iodine use contraversia

- Although there are sparse clinical data relating to radioactive iodine use in children with GD and subsequent thyroid cancer, it is known that risks of thyroid cancer after external irradiation are highest in children <5 years of age, and they decline with advancing age.
- In comparison, activities of radioactive iodine used with contemporary therapy are not known to be associated with an increased risk of thyroid neoplasm in children. (1,2)

Long-term follow-up (36 y) of over 100 children who were treated with radioactive iodine before age 20 years revealed no increase in the rates of thyroid cancer or birth defects in offspring of these children. (3)

Side-effects of 131I therapy in children

- Side effects of 131I therapy in children are uncommon apart from the lifelong hypothyroidism that is the goal of therapy.
- Less than 10% of children complain of mild tenderness over the thyroid in the first week after therapy.
- It can be treated effectively with acetaminophen or nonsteroidal anti-inflammatory agents for 24–48 hours.

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When surgery is the planned therapy and MMI cannot be administered:
- if the patient is not too thyrotoxic (and the hyperthyroidism is due to GD), the hyperthyroid state can be controlled before surgery with beta blockade and SSKI (50 mg iodide/drop) 3–7 drops (0.15–0.35 mL) by mouth, given three times a day for 10 days before surgery.

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Surgery

- Thyroidectomy is an effective treatment for GD,
- but is associated with a higher complication rate in children than adults
- Thyroidectomy should be performed in those children who are too young for radioactive iodine
- provided that surgery can be performed by a high-volume thyroid surgeon, preferably with experience in conducting thyroidectomies in children. (1,2)

Thyroidectomy is the preferred treatment in:

- for GD in young children (<5 years) when definitive therapy is required
- In individuals with large thyroid glands (>80 g) that the response to 131I may be poor

Hyperthyroidism Management Guidelines, *Endocr Pract.* 2011;17(No. 3)
If thyroidectomy is chosen as treatment for GD in children, how should it be accomplished?

- Children with GD undergoing thyroidectomy should be rendered euthyroid with the use of methimazole.
- Potassium iodide should be given in the immediate preoperative period.
- MMI is typically given for 1–2 months in preparation for thyroidectomy.
- Ten days before surgery, potassium iodide (SSKI; 50 mg iodide/drop) can be given as 3–7 drops (i.e., 0.15–0.35 mL) three times daily for 10 days before surgery.

Total or near-total thyroidectomy should be performed, since subtotal thyroidectomy is associated with a high risk of relapse in this group.

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Surgical complication rates are higher in children than in adults, with higher rates in younger than in older children (194). Postoperatively, younger children also appear to be at higher risk for transient hypoparathyroidism than adolescents or adults (194).

More experienced surgeons can reduce the risk of complications. The two most common complications are:

- **Hypoparathyroidism**: damage to the parathyroid glands that control calcium
- **Recurrent laryngeal nerve damage**: nerves that control the voice and help to protect the airway so that food, liquid or other items do not enter the lungs

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The END

Thank you!