Adrenal Insufficiency (AI)

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Adrenal Insufficiency (AI)

Objectives
- Physiology
- Etiology
- Signs and Symptoms
- Diagnostic Testing
- Treatment

Adrenal Hormones

Glucocorticoids
- Hydrocortisone
- Cortisol
- DHEA
- 17-OH Prog.
- 17α-OH Prog.
- 21-Hydroxylase
- 11-Deoxycortisol
- Androstenedione
- Testosterone
- 17α, 20α-Lyase
- Estrone
- Estrogen
- Aromatase
- Mineralocorticoids
- Aladosterone
- Cortisol

Feedback Mechanism

- Renin Angiotensin
- ACTH
- Cholesterol
- Aldosterone
- Cortisol

Adrenal Insufficiency Physiology

- Primary AI: Results from disease intrinsic to the adrenal cortex.
- Secondary AI: Results from deficient secretion of ACTH by the pituitary gland.
- Tertiary AI: Results from deficient secretion of hypothalamic CRH or other ACTH secretagogues.
- NOTE: Secondary & Tertiary AI are placed in one category: Central Adrenal Insufficiency.

Central Adrenal Insufficiency

- Isolated ACTH deficiency: mutations in TPIT, POMC, PCI genes.
- Congenital hypopituitarism: mutations in PROP1, HESX1, LHX4.
- Tumors: craniopharyngioma, dysgerminoma.
- Tumor treatment: surgery, irradiation.
- Congenital malformations: empty sella.
- Anencephaly, Septo-Optic Dysplasia, other midline defects.
Central Adrenal Insufficiency (cont)
- Infiltrative diseases: Histiocytosis X, Sarcoidosis, Hemochromatosis
- Trauma
- Infections: meningitis, encephalitis.
- Cessation of glucocorticoid therapy or ACTH therapy, megestrol acetate.
- Removal of a unilateral adrenal tumor with suppression of other side.
- Infants born to mothers treated with glucocorticoids (rare).

Primary Adrenal Insufficiency
Adrenal Dysgenesis
- Gene Defects
  - ACTHR/MC2R
  - MRAP
  - DAX-1/NROB1
  - SF-1/NR5A1
  - IMAGe Syndrome

Primary Adrenal Insufficiency
Impaired Steroidogenesis
- Steroid pathway
  - CAH, POR
- Cholesterol pathway
  - SLO Syndrome
- Drugs:
  - Ketoconazole
  - o,p’DDD (mitotane)
  - Rifampin
  - Etomidate, Aminoglutethimide

Etiology of Primary AI (Addison’s) Overview
- Adrenal Dysgenesis
- Adrenal Gland Destruction
- Impaired Steroidogenesis
- Medication Induced AI

Primary Adrenal Insufficiency
Adrenal Destruction
- Autoimmune
- Adrenal hemorrhage
- Tumors
- Infection
- Infiltrative disorders
- Bilateral adrenalectomy
- Peroxisomal/Lysosomal Disorders.

Congenital Adrenal Hyperplasia
- Group of autosomal recessive disorders
- Common feature is an enzymatic defect in the steroidogenic pathway leading to the biosynthesis of cortisol: \( \downarrow \text{Cortisol} \rightarrow \uparrow \text{ACTH} \rightarrow \) adrenal hyperplasia.
- More appropriately referred to by the names of the specific deficiencies involved.
- Phenotypes determined by which hormones are deficient and/or in excess.
**Congenital Adrenal Hyperplasia**

- 21 Hydroxylase: 95%
- 11β Hydroxylase: 5–8%
- 3β HSD: 2.4%
- 17α hydroxylase: < 1%
- StAR/Lipoid: < 1%

**Adrenal Hypoplasia Congenita (AHC)**

- Defect in adrenal cortical development.
- Deficiency of glucocorticoids, mineralocorticoids, and adrenal androgens.
- Appears in infancy.
- Two forms:
  - X-Linked form with very large adrenocortical cells.
  - Sporadic recessive form with miniature cells.

**Adrenal Hypoplasia Congenita (AHC) (cont.)**

- X-Linked Form: Due to gene defect NROBI expressed in the hypothalamus, pituitary gonadotrophs, adrenals, and testes.
- Encodes for a nuclear receptor DAX-1.
- Infant males get microphallus and adrenal insufficiency.
- A contiguous gene deletion syndrome including the gene for Duchenne Muscular Dystrophy (DMD), glycerol kinase gene (GK), and ornithine transcarbamylase gene (OTC) can give rise to other symptoms.

**Primary Adrenal Insufficiency**

**Idiopathic Autoimmune Adrenalitis**

- Onset: mid-childhood, adolescence
- HLA – DR/DQ
- Associated disorders: rare
- Sporadic inheritance
- Anti-adrenal antibodies: present
- Anti-steroidal cell antibodies: rare

**Autoimmune Polyendocrinopathy Syndrome Type 1 (APS1)**

- APS1: Autoimmune Polyendocrinopathy candidiasis and ectodermal dystrophy (APECED).
- Autosomal recessive: childhood onset.
- Chronic Mucocutaneous Candidiasis: 73–100%
- Hypoparathyroidism: 90%
- Primary Adrenal Insufficiency: 60-80%
- Ectodermal dysplasia: 77%

**Autoimmune Polyendocrinopathy Syndrome Type 1 (APS1) (cont.)**

- Condition may be associated with: chronic active hepatitis, malabsorption, alopecia, pernicious anemia, vitiligo, hypogonadism, primary hypothyroidism.
- Mutations in the AIRE gene, an autoimmune regulator gene.
- No HLA association
- Positive for anti-adrenal cell antibodies.
- Positive for anti-steroidal cell antibodies.
Autoimmune Polyendocrinopathy Syndrome Type 2 (APS 2)

- Onset: Childhood – Adulthood
- Autosomal dominant – incomplete penetrance
- Female predominance: 3:1
- HLA-DR/DQ
- Adrenal Insufficiency: 100%
- Auto-immune thyroid disease: 70%
- Type I DM: 52%

Autoimmune Polyendocrinopathy Syndrome Type 2 (APS 2) (cont.)

- Anti-adrenal antibodies: present
- Anti-steroid cell antibodies: rare
- Other Associated disorders: pernicious anemia, myasthenia, gravis, vitiligo, alopecia, immune thrombotic cytopenic purpura

Autoimmune adrenal insufficiency in children

<table>
<thead>
<tr>
<th>Autoimmune polyendocrinopathy syndrome type 1</th>
<th>Autoimmune polyendocrinopathy syndrome type 2</th>
<th>Isolated autoimmune adrenals</th>
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</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>50%</td>
<td>20%</td>
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<tr>
<td>Age at onset</td>
<td>Young, early childhood</td>
<td>Mild, adolescence</td>
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<td>Gender distribution</td>
<td>Male: Female</td>
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<tr>
<td>Associated Disorders</td>
<td>Hyperparathyroidism</td>
<td>Autoimmune thyroid disease</td>
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<tr>
<td>Antiadrenal antibodies</td>
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<tr>
<td>Antibasal antibodies</td>
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<td>Rare</td>
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<td>Major Manifestations</td>
<td>Loss of function in AEP</td>
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<tr>
<td>Primary Afflict</td>
<td>ABCD1</td>
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</table>


Hyperpigmentation of the oral mucosa

Primary Adrenal Insufficiency: Adrenoleukodystrophy (ALD)

- X-Linked
- Incidence: 1:20,000
- Defective ABCD1 gene/ALDP protein
- Defective beta oxidation of very long chain fatty acids (VLCFA’s)
- Inflammatory demyelinating process: involves cerebral hemispheres in young and adolescent boys.
Primary Adrenal Insufficiency: Adrenoleukodystrophy (ALD) (cont.)

- Adrenal insufficiency may predate, occur simultaneously, or follow the onset of neurological deficits.
- Approximately 10% of ALD patients present with Addison’s disease alone, usually young boys less than 8 years.
- Plasma VLCFA’s should be done in all males with idiopathic primary AI.
- Approximately 20% of women carriers have a milder form of AI and/or CNS disease.

Adrenal Insufficiency Adrenomyeloneuropathy

- Non-inflammatory distal axonopathy: long tracts of spinal cord and peripheral nerves.
- Predominance: males, ages 20-40.
- Slowly progressive paraparesis.
- May or may not involve cerebral hemispheres.
- Check plasma VLCFA’s in all males with primary AI and in men with progressive paraparesis.

Adrenal Insufficiency Clinical Manifestations

Mineralocorticoid Deficiency

- Muscle weakness
- Fatigue
- Weight loss
- GI Symptoms: nausea, vomiting, diarrhea
- Salt Craving
- Postural dizziness
- Hypotension, decreased BP, decreased blood volume → shock

Adrenal Insufficiency Clinical Manifestations (cont.)

Glucocorticoid Deficiency

- Fasting Hypoglycemia
- Increased insulin sensitivity
- Decreased gastric acidity
- Gastrointestinal symptoms: nausea, vomiting
- Fatigue
- Headache
- Myalgia’s, arthralgia’s
- Decreased cardiac output; Decreased peripheral vascular resistance → CV collapse

Adrenal Insufficiency (AI) Clinical Features

Androgen Deficiency

- Decreased axillary hair & pubic hair
- Decreased libido

Increased Pituitary ACTH & MSH

- Hyperpigmentation

Primary Adrenal Insufficiency

- Hyperpigmentation
- Hyponatremia
- Hyperkalemia
- Metabolic Acidosis

Central Adrenal Insufficiency

- Normal Sodium or Mild Hyponatremia
- No Hyperkalemia
- No Metabolic Acidosis
- No Hyperpigmentation
Adrenal Insufficiency (AI)
Diagnostic Testing/Evaluation

- Baseline Studies:
  - 8 AM Cortisol, ACTH
  - Fasting glucose
  - VBG
  - Electrolytes, CMP
  - Plasma renin activity
  - Aldosterone level
  - Other: EKG changes

Factors Influencing Glucocorticoid Dose

- Cortisol production rate
  - Physiologic unstressed
    - 5-10 mg/m²/day
- Variables affecting cortisol kinetics:
  - Weight
  - Height
  - Body Surface Area (BSA)
  - Individual metabolism/clearance
- Recommend weight or BSA adjusted H.C. dose.
- Recommend double the production rate due to 50% absorption.

Adrenal Insufficiency
Treatment: Maintenance Therapy

- Warning: Do not increase dose of H.C. for emotional stressful days, common cold, exercise.
- Surgery: Patient will require careful pre-operative management with H.C. prior to surgery and procedures requiring sedation or anesthesia. Stress Dose: H.C. 75 – 100 mg/m² X 1 with induction of anesthesia; then, stress dose divided Q6h until stress subsides (usually 24h).

Mineralocorticoid Treatment. Monitor for:
- Orthostatic Hypotension
- Edema
- Salt craving
- K+ and NA
- Maintain plasma renin levels at mid – upper range of normal
**Glucocorticoid Therapy.**  Monitor ACTH levels:
- ACTH levels elevated prior to AM glucocorticoid dose (in primary AI)
- ACTH levels decline rapidly with increasing cortisol levels after dose.
- Aiming for ACTH levels in the normal range will lead to over replacement.
- Aim for ACTH levels < 2-3 times upper limit of normal.

**Adrenal Insufficiency (AI) Etiology of Adrenal Crisis**
- Underlying Adrenal Insufficiency → Acute Precipitant → Adrenal Crisis
- Precipitants of Adrenal Crisis:
  - Surgery
  - Medical Procedures
  - Anesthesia
  - Infections
  - Alcohol / Drugs
  - Hypothermia
  - MI, CVA, PE

**Acute AI: Clinical Features**
- Dehydration, volume depletion.
- Hypotension → Circulatory Collapse → Shock
- Coma/Seizures
- Abdominal Pain
- Fever
- Weakness, apathy, depressed mentation.
- Hypoglycemia
- Hyponatremia
- Hyperkalemia

**Adrenal Crisis**
Adrenal Crisis may occur in the following situations:
- Patients with an undiagnosed primary adrenal disease who is subjected to serious illness or major stress.
- Patients with known primary adrenal insufficiency who do not take stress dosage of glucocorticoids during an illness or in patient with persistent vomiting.

**Adrenal Crisis (cont’d)**
- Patients who are critically ill with septic shock and who are unresponsive to fluid resuscitation and inotropic medications.
- Patients who are withdrawing from chronic steroid use.
- Less frequently in patients with secondary or tertiary adrenal insufficiency during acute stress or pituitary infarction.

**Adrenal Hemorrhage**
- Overwhelming sepsis (Waterhouse – Friderichsen Syndrome)
- Trauma or surgery.
- Anti-coagulant therapy.
- Coagulopathy
- Adrenal tumors or adrenal metastases.
- Spontaneous: eclampsia, post-partum complications.
Adrenal Crisis: Diagnostic Evaluation

- Random Cortisol
- ACTH
- Electrolytes
- Glucose
- CMP
- VB6
- CBC + Diff: Normochromic, Normocytic, Eosinophilia.

Adrenal Crisis: Treatment

- Fluid push with normal saline or lactated ringers at 10 – 20 cc’s/kg over 30 – 60 min. May need to repeat.
- Follow with 5% dextrose in normal saline or ½ normal saline.
- Stress Hydrocortisone 75 – 100 mg/m² x 1 IV then divide and give Q6h.
- Specific mineralocorticoid replacement is not required as high doses of glucocorticoids have mineralocorticoid effects.

Adrenal Crisis: Treatment (cont)

- Monitor electrolytes, glucose, BUN.
- Once the dose of glucocorticoids is reduced and patient tolerating fluids, fludrocortisone can be restarted.
- Investigate and treat the precipitant.

Patient Education

- Patients/parents should be educated about:
  - need for life long therapy.
  - stress dosing during illness and/or surgery.
  - wearing a medical alert bracelet or necklace.
  - seeking immediate medical assistance if symptoms worsen so that parenteral glucocorticoid therapy may be administered.
- Endocrinologists must provide patients and/or parents with emergency instruction letter for carrying to ED.
Hypocalcemia in infants and children

John Buchlis MD

Calcium Homeostasis

- Extracellular calcium [Ca]:
  - Critical for cell function and survival
  - Is controlled by fluxes of calcium between
    - Extracellular fluid and skeleton
    - Gut and kidney

• These fluxes are regulated by:
  - Calcium sensing receptor [CaSR] – PTH
  - 1,25 dihydroxy vitamin D
  - Calcitonin

CaSR

• Calcistat – on parathyroid gland
  - Senses the serum ionized calcium
  - Triggers release of PTH even with minute decrease of ionized calcium [iCa]
  - PTH release is suppressed when iCa is high

PTH

Synthesized in chief cells of parathyroid gland

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<th>INTESTINE</th>
<th>KIDNEYS</th>
<th>NET EFFECT</th>
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<td>↓</td>
<td>↑</td>
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<tr>
<td>PHOSPHORUS</td>
<td>↑</td>
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Calcitonin

Synthesized and secreted by parafollicular cells of thyroid

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<thead>
<tr>
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1,25dihydroxy VitD
Active metabolite of vit D

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<th>KIDNEYS</th>
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Definition of Hypocalcemia

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<tr>
<th>NEONATES</th>
<th>Ca (mg/dl)</th>
<th>ICa (mg/dl)</th>
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<tr>
<td>BW &lt;1500gm</td>
<td>&lt;7</td>
<td>&lt;4.6</td>
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<tr>
<td>&gt;1500gm</td>
<td>&lt;8</td>
<td>&lt;4.4</td>
</tr>
<tr>
<td>TERM INFANTS</td>
<td>&lt;8</td>
<td>&lt;4.4</td>
</tr>
<tr>
<td>CHILDREN</td>
<td>&lt;8.5</td>
<td>&lt;4.8</td>
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Neonatal Hypocalcemia

- Early : in first 3 days of life
- Late : After 3 days of life

Early Neonatal Hypocalcemia

- 1. Prematurity and low birth weight
  - Delayed maturation of Vit D pathways
  - ↓ intestinal Ca absorption and mobilization from bones
  - ↑ Ca demand by growing skeleton
  - Reduced total Ca stores
  - Limited PO intake in sick babies

Other causes of Early Neonatal Hypocalcemia

- Maternal hyperparathyroidism
- Severe respiratory alkalosis
  - In hyperventilated infants
- Citrates
  - Chelates Ca- blood transfusions

Early Neonatal Hypocalcemia

2. Birth Asphyxia
   - Excess release of phosphorus from cellular damage
   - ↑ Calcitonin release
   - Use of alkali for resuscitation
   - Limited milk and Ca intake

3. Infants of diabetic mother
   - Magnesium deficiency
     - ↓ PTH secretion and induces resistance to PTH
   - Reduced PTH secretion
   - All other factors mentioned before and often born prematurely and asphyxiated
Late Neonatal Hypocalcemia: After 3 days of life

• Hypoparathyroidism
  – Maternal hypercalcemia
  – DiGeorge syndrome
  – PTH gene mutations

• Phosphorus overload
  • (↑ Ca deposition in bones + relative resistance to PTH)
    – Cow’s milk
    – Fleet enema
    – Renal failure (↓ calcitriol synthesis)

Hypocalcemia beyond the neonatal period

• Hypoparathyroidism
  • ↓Ca, ↑ P, ↑PTH
• Pseudohypoparathyroidism
  • ↓Ca, ↑ P, ↑PTH
• Hypomagnesemia
• Vitamin D deficiency-Nutritional
  • Normal or ↓ Ca, ↓ P, ↓ PTH, ↑ ALP, ↓ 25(OH)D and normal or high 1,25(OH)2D
• Critical illness
• GI loss
• Mediation
  • Chelators- citrate
  • Bisphosphonates reduces osteoclast resorption
  • Furosamide- induces calcitriol
• Acute pancreatitis- calcium deposition + glucagon stimulated calcitonin release

Vitamin D Deficiency

• Vit D deficiency
  – Dietary absence / Malabsorption
• Accelerated loss
  – Impaired enterohepatic recirculation / Anticonvulsants
• Impaired 25-hydroxylation
  – End stage liver disease / INH
• Impaired 1α hydroxylation
  – Renal failure
• Target organ resistance
  – Vit D dep rickets type 2 / Phenytoin

Clinical Presentation

• Nervous system
  – Mild hypocalcemia – hyperreflexia
  – Moderate – muscle cramps, paresthesias of hands, feet, perioral area
  – Severe- tetany, seizures, laryngospasm
    • Chvostek’ sign
    • Trousseau sign

Labs

• CMP
• PTH
• Magnesium
• 25(OH) vit D
• 1,25 dihydroxy vit D
• Amylase + Lipase
• Urine Ca + Creatinine
Treatment

- Symptomatic hypocalcemia:
  - 2ml/kg of 10% Calcium Gluconate IV over 10 minutes, Q6-8hrs prn
    - EKG monitoring for QT interval changes
    - Cardiac monitoring for hypotension and bradycardia
    - Avoid scalp and peripheral veins as extravasation causes tissue necrosis

Post symptomatic Hypocalcemia

- IV:
  - 50-100mg elemental Ca/kg/day ÷ Q6hrs
    - 5-10ml of 10% Ca Gluconate/kg/day ÷ Q6 or continuous diluted in IV fluids
- Oral:
  - 50-100mg elemental Ca/kg/day ÷ Q6
    - CaCO3 0.5-1ml/kg/day
- Vit D for older babies with persistent hypocalcemia
  - Rocaltrol 0.5-2mcg Po daily or IV 0.05mcg/kg/day x 5days if symptomatic

Treatment continued

- Hypomagnesemia
  - For emergencies [seizures]
    - 20-100mg/kg/dose Mag sulfate q4-6hrs prn IV/IM
  - Nonemergencies
    - Neonates: 25-50mg/kg/dose (0.2-0.4meq/kg/dose) q8-12hrs for 2-3 doses IV
    - Children: 100-200mg/kg/dose (10-20mg elemental mag/kg/dose) PO QID OR
    - 25-50mg/kg/dose q4-6hrs IV/IM for 3-4 doses, max single dose 16meq=2grs

Graves Disease

- Most common cause of thyrotoxicosis in children and adolescents
- Incidence – 1: 10,000 children
- May begin in infancy
- Incidence increases sharply in adolescence
- 6-8 times more common in females
- Has a genetic basis
- Graves and Hashimotos arise randomly in a genetically predisposed population

Pathogenesis

- TSH stimulating immunoglobulin (TSI) plays a major role
  - It displaces TSH from membrane TSH receptors
  - Stimulates adenylate cyclase and cyclic AMP production in thyroid follicular cells
- Production of TSI by B-lymphocytes is a secondary response involving T-lymphocytes
Clinical Features

• Insidious onset
  – Increasing nervousness, palpitations, weight loss despite increased appetite, muscle weakness
• Size of thyroid gland is highly variable
• Exophthalmos is present in 1/3rd of children
• Staring (retraction of upper lid by sympathetic hyperactivity)

Laboratory Diagnosis

• ↑ Free T4
• ↑ T4
• ↑ Total T3
• Suppressed TSH (usually <0.04mu/l)
• ↑ TSI
• ↑ 24hr uptake

Neonatal thyrotoxicosis

• Placental transfer of maternal TSH receptor antibodies (TRABs)
  – TRABs can inhibit thyroid hormone production (TBII)
  – Can stimulate thyroid hormone production (TSI)
• TSI may persist in a mother even:
  – Post surgical
  – Medical ablation of thyroid gland

Neonatal thyrotoxicosis

• Rare causes:
  – McCune Albright syndrome
  – Activating mutation of TSH receptor
• Is associated with:
  – Fetal loss
  – Prematurity
  – IUGR
  – High mortality rate (12-20%)-usually from heart failure

Clinical Presentation

• Usually presents within first ten days of life
• Delayed presentation, if coexisting maternal stimulating and blocking antibodies
• Signs and Symptoms:
  – Poor feeding, vomiting, weight loss
  – Irritability
  – Tachycardia, bounding pulses, arrhythmia, HTN, heart failure-cardiovascular compromise being main cause of mortality
### History
- **Risks for neonatal thyrotoxicosis:**
  - If mother has past history of thyrotoxicosis
  - Presence and titers of maternal TSI in 3rd trimester (>350%, normal is 130%)
- **Maternal TSI is cleared in the newborn within 3 months after birth**
- **Breast feeding**
  - Is permitted unless mother is on high doses of antithyroid meds
  - Could worsen neonatal thyroid disease secondary to transfer of TRABs in breast milk

### Physical Examination
- Goiter
- Eye signs [exophthalmos, lid retraction]
- Craniosynostosis, cerebral ventricular enlargement, microcephaly
- Metabolic effects: diarrhea, sweating, flushing
- Hepatomegaly, thrombocytopenia

### Investigations
- T3, T4, FreeT4, TSH immediately after birth and close monitoring in 1st week of life
- TSI or TBII
- Thyrotoxicosis could be delayed for few days if mother was on antithyroid medications
- ECHO for heart failure

### Management
- **Carbimazole or Methimazole**
  - Inhibit thyroid peroxidase
  - Initial dose 0.25mg/kg TID
- **Propanolol**
  - ↓ HR, ↓ BP, ↓ myocardial contractility
  - Inhibits peripheral conversion of T4 to T3
  - Initial dose 0.25mg/kg Q6H

### THYROID STORM
- One of the most critical endocrine emergencies
- Reflects the extreme manifestation of thyrotoxicosis
- Incidence <10% of patients admitted for thyrotoxicosis
- Untreated thyroid storm is fatal
- Mortality rate 20-30%

### Management
- **Potassium iodide - Lugol’s solution**
  - 8.3mg iodine per drop
  - Raises plasma iodide concentrations
  - Inhibits iodide organification
  - Most rapidly effective treatment
  - Neonatal dose 0.05-0.1ml TID
- **Glucocorticoids**
  - Short term treatment
  - Inhibit peripheral conversion of T4 to T3
  - Inhibit thyroid hormone secretion
• Most common underlying cause of thyroid storm is:
  – Graves disease (untreated or partially treated)
  – Can also occur with a solitary toxic adenoma
  – Or a toxic multinodular goiter

• Rare causes of thyrotoxicosis leading to storm:
  – Hypersecretory thyroid carcinoma
  – TSH secreting pituitary adenoma
  – A-interferon, interleukin-2 for viral hepatitis and HIV
  – Hyperthyroidism aggravated by iodine exposure (contrast dye or amiodarone)

• Hypothesis
  • Increase of free thyroid hormones:
    – Free T4 levels higher in storm patients than thyrotoxicosis
      • (Brooks and colleagues)
    – Total T4 was similar
    – No arbitrary cutoff values for T3 or T4 to differentiate storm from thyrotoxicosis
    – Thyroid storm is a clinical diagnosis
  • Diagnostic criteria by Burch and Wartofsky scale
    – It is best to treat aggressively rather than trying to find out if patients meet the criteria for storm

• Triggers
  • In the past:
    – Thyroid surgery in patients with uncontrolled hyperthyroidism
  • Now:
    – Severe infection or sepsis
  • Other:
    – Trauma
    – MI
    – DKA
    – Pulmonary thromboembolism
    – Radioiodine therapy
    – Pseudoephedrine and salicylates (↑ Free T4 levels)

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<th>SCORING</th>
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<td>CNS EFFECTS</td>
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<tr>
<td>Mild (agitation)</td>
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<tr>
<td>Moderate (delirium, psychosis, extreme lethargy)</td>
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<tr>
<td>Severe (seizures, coma)</td>
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<tr>
<td>GI-HEPATIC DYSFUNCTION</td>
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<tr>
<td>Moderate (diarrhea, nausea/vomiting, abdominal pain)</td>
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<tr>
<td>Severe (unexplained jaundice)</td>
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<table>
<thead>
<tr>
<th>CARDIOVASCULAR DYSFUNCTION: Tachycardia</th>
</tr>
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<tbody>
<tr>
<td>110-119</td>
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<td>120-129</td>
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<tr>
<td>140</td>
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<tr>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>Absent</td>
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<tr>
<td>Mild (pedal edema)</td>
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<tr>
<td>Moderate (bibasilar rales)</td>
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<tr>
<td>Severe (pulmonary edema)</td>
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<tr>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>Absent</td>
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<tr>
<td>Present</td>
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<tr>
<td>Precipitating event</td>
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<tr>
<td>Absent</td>
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<tr>
<td>Present</td>
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• Other lab findings:
  – Hyperglycemia
    • Increased glycogenolysis
    • Catecholamine inhibition of insulin release
  – Hypercalcemia (bone resorption)
  – Leukocytosis and elevated liver enzymes
  – High serum cortisol (stress)

– A score of ≥ 45 → highly suggestive of thyroid storm
– Score of 25-44 → suggestive of impending storm
– Score of <25 → unlikely to represent storm
Management

- These patients require aggressive treatment in ER and continued care in ICU

Inhibition of new hormone production:

- 1st line therapy
- Methimazole
  - 20-25mg Po q6hr
- Propylthiouracil
  - Not recommended for children due to hepatotoxicity
  - Also ↓T4-T3 conversion
  - 200-400mg PO q6-8hr

Inhibition of thyroid hormone release:

- Administer at least 1hr after thionamide
- Potassium iodide SSKI
  - 5drops PO q6hr
- Lugol’s solution
  - 4-8drops PO q6-8hr
- Sodium ipodate (308mg iodine/500mg tab)
  - 1-3g PO qd
  - Also inhibits T4-T3 conversion
- Iopanoic acid
  - 1g PO q8hr for 24 hrs then 500mg PO q12hr
  - Also inhibits T4-T3 conversion

Beta-adrenergic blockade:

- Propanolol
  - 60-80mg Po q4hr OR 80-120mg q6hr
  - Also ↓T4-T3 conversion
- Cardioselective agents:
  - Atenolol: 50-200mg PO qd
  - Metoprolol: 100-200mg PO qd
  - Nadolol: 40-80mg PO qd
- IV: when oral agents not indicated or consider in CHF
- Esmolol: 50-100μg/kg/min

Supportive treatment:

- Acetaminophen
  - For hyperthermia, preferred over salicylates
  - 325-650mg PO/PR q4-6hr prn
- Hydrocortisone
  - When hypotensive to treat possible concomitant adrenal insufficiency
  - ↓T4-T3 conversion and for vasomotor stability
  - 100mg IV q8hr

Alternate therapies:

- Lithium carbonate
  - Used when thionamide or iodide therapy contraindicated; levels should be checked
  - Blocks release of hormone + inhibits new hormone synthesis
  - 300mg PO q8hr
- Potassium perchlorate
  - Used in combination with thionamide in type II amiodarone induced thyrotoxicosis
  - Inhibits iodide uptake by gland
  - 1g PO qd
- Cholestyramine
  - Used in combination with thionamide
  - Reduces reabsorption of thyroxine from enterohepatic circulation
  - 4g PO qid

Thank you