THYROTOXIC CRISIS

INTRODUCTION (KATRINA KNAPP, D.O., 4/2016)
Thyrotoxicosis is the clinical manifestation of hyperthyroidism. Thyrotoxic crisis, otherwise known as thyroid storm, is a life threatening condition that involves multi-organ system dysfunction including severe cardiovascular, thermoregulatory, gastrointestinal, and neurobehavioral symptoms. It is seen in less than 1% of adults with hyperthyroidism and is rarer in children. It has a high mortality rate (10-30%) if not recognized early and treated aggressively.

PATHOPHYSIOLOGY
Thyroid hormones are produced in the thyroid gland under the influence of thyroid stimulating hormone (TSH). Thyroid releasing hormone (TRH) from the hypothalamus stimulates TSH release from the pituitary. In order to maintain thyroid hormone levels in normal range, circulating levels of thyroid hormones exert feedback inhibition on the hypothalamus and pituitary axis (HPA).

There are 2 active thyroid hormones: triiodothyronine (T3) and L-thyroxine (T4). T4 is exclusively made in the thyroid gland. T3 is also made in the thyroid but 80% is made in the peripheral tissues by de-iodination of T4. Iodine is essential for thyroid hormone synthesis.

T4 is more abundant than T3 and a greater proportion is protein bound (e.g. TBG, thyroid binding globulin). Only 0.03% of T4 is unbound. It is the unbound ("free") hormones that are active. A greater proportion of T3 is the free form, and has a greater affinity (10 fold) for tissue thyroid hormone receptors than T4. T4 can also be metabolized to reverse T3 which is completely inactive. Most of the biologic activity of thyroid hormones is due to T3, but it is less reliably identified which is why we typically measure free T4.

Thyroid hormones increase oxygen consumption in all tissues except the brain, spleen, and testes. They also stimulate adrenergic receptors sites in myocardial cells and glucocorticoid receptors in lung tissue. In addition, thyroid hormones accelerate the metabolism of other hormones (insulin, cortisol).

Thyrotoxicosis can develop in patients with longstanding untreated hyperthyroidism or it can be precipitated by an acute event (see table below). Thyroid storm is a hyper-metabolic and beta-adrenergic driven state. Over production of thyroid hormones increase the density of beta-adrenergic receptors enhancing the effect of catecholamines. 90% of thyrotoxicosis is caused by hyperthyroidism. The most common cause in children is Grave's Disease. Grave's disease is an autoimmune disorder that results in antibody production (TSH receptor stimulating immunoglobulins) that stimulate TSH receptors resulting in excessive stimulation of the thyroid gland.

COMMON CAUSES/PRECIPITATING FACTORS OF THYROTOXICOSIS
Primary hyperthyroidism (Grave's disease, toxic multi-nodular goiter)
Secondary hyperthyroidism (pituitary adenoma)
Thyroiditis (postpartum, radiation thyroiditis)
Drug Induced (lithium, iodine, amiodarone, excessive thyroid hormone ingestion, anticholinergic drugs, adrenergic drugs)
Abrupt cessation of anti-thyroid medications
Thyroid or non-thyroid surgery in a patient with unrecognized hyperthyroidism
Acute illness (diabetic ketoacidosis, sepsis), labor and delivery
Trans-placental passage of maternal thyroid stimulating immunoglobulins

CLINICAL MANIFESTATIONS

The diagnosis of thyrotoxic crisis is based upon the presence of severe life threatening symptoms (cardiovascular dysfunction, altered mental status, hyperpyrexia) in a patient with biochemical evidence of hyperthyroidism.

PRESENTATION	
Metaboli	Fever, sweating, metabolic acidosis, hyperventilation, amenorrhea, weight loss
GI	Nausea, vomiting, diarrhea, abdominal pain, hepatic dysfunction
Cardiac	Sinus tachycardia out of proportion to the degree of fever Hypotension, congestive heart failure Atrial fibrillation (up to 20% of adults, rare in children), Prolonged QT interval
Neuro-Psychiatric	Agitation, delirium, psychosis, stupor, coma
Newborns	Irritable, unable to feed appropriately, and have inadequate weight gain.

DIFFERENTIAL DIAGNOSIS	
Endocrine	Pheochromocytoma, adrenal crisis
Infections	Sepsis, gastroenteritis
Toxicologic	Hyperpyrexia syndromes: malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome
	Anticholinergics, Sympathomimetics (cocaine, amphetamine)
	Medication withdrawal: cocaine, opiates
Environmental	Heat stroke
Psychiatric	Anxiety/panic attack

PHYSICAL EXAMINATION	
Eyes	Staring appearance due to upper eyelid retraction, eyelid lag (both due sympathetic over-activity). Light sensitivity
	Grave's ophthalmopathy (periorbital edema, proptosis) is an autoimmune mediated inflammation and edema of extraocular muscles and intra-orbital connective tissue. 50-70% of children.
Neck	Smooth, diffusely and symmetrically enlarged goiter. No palpable nodularity. Typically, non-tender to palpation. Bruit over a large vascular gland possible
Cardiac	Most common cardiac finding is sinus tachycardia. Heart failure and arrhythmia (atrial fibrillation) more common in adults. High cardiac output produces bounding pulse, widened pulse pressure.
Skin	Warm (cutaneous vasodilation) and moist (diaphoresis)
	Grave's dermatopathology (bilateral non-pitting edema with associated thickening and induration of the skin) Typically seen over the ankles and feet. Rare in children
Neuro	Altered mental status, hand tremor, agitation, psychosis, hyperreflexia,

A clinical scoring system for diagnosing thyroid storm was published (See table below, Burch, Endo-Metab Clinics of NA 1993, PUBMED ID: 8325286) but has not been validated.

POINT SCALE FOR THE DIAGNOSIS OF THYROID STORM			
TEMPERATURE		GASTROINTESTINAL DYSFUNCTION	
99.0-99.9	5	Absent	0
100.0-100.9	10	Moderate (N,V,D, abd pain)	10
101.0-101.9	15	Severe (Jaundice)	20
102.0-102.9	20	PRECIPITANT HISTORY	
103.0-103.9	25	Positive	0
≥ 104.0	30	Negative	10
TACHYCARDIA		CNS DYSFUNCTION	
100-109	5	Absent	0
110-119	10	Mild (Agitation)	10
120-129	15	Moderate*	20
130-139	20	Severe (Seizure, Coma)	30
≥ 140	25	*Delerium, psychosis, severe lethargy	
ATRIAL FIBRILLATION			
Absent	0		
Present	10		
CONGESTIVE HEART FAILURE			
Absent	0	**TOTAL SCORE**	
Mild	5	THYROID STORM	> 45
Moderate	10	IMPENDING STORM	24-44
Severe	20	STORM UNLIKELY	< 25

LABORATORY TESTING

Laboratory findings are consistent with primary hyperthyroidism (Low TSH, high free T4/T3). Values are similar to those seen in uncomplicated hyperthyroidism. Abnormal liver function tests (thyroid hormones play a role in the metabolism of bilirubin) and an elevated glucose (catecholamine induced inhibition of insulin and increase glycogenolysis), elevated calcium (increased bone resorption) and leukocytosis or leukopenia may be seen.

MANAGEMENT

Initially treatment is directed at inhibiting the peripheral effects of thyroid hormone and decreasing metabolic rate and cardiac workload. Subsequent treatment is directed at decreasing thyroid hormone production, inhibiting release and enhancing clearance as well as recognition and treatment of precipitating factors. The patient should be admitted to an ICU to monitor for clinical deterioration and to provide ongoing care. See also: Hyperthyroidism Guidelines: American Association of Clinical Endocrinologists 2011: PUBMED ID: 21700562

INITIAL STABILIZATION
Airway protection, oxygenation, ventilation PRN
EKG, cardiac monitoring, avoid medications that can prolong the QT interval
Supportive measures including aggressive cooling e.g. cooling blankets
Fluid resuscitation (increased insensible fluid losses)
Acetaminophen for temperature regulation*
Decrease metabolic rate: Beta blockers (e.g. Propranolol)
Decrease thyroid hormone production: Methimazole, Propylthiouracil, Iodine
Consider corticosteroids, bile acid sequestration (e.g. Cholestyramine)
Treatment of precipitating factors
Admit to Intensive Care Unit
*DO NOT GIVE ASPIRIN: Increases T4 by displacing thyroid hormone from protein binding and increase metabolic demand by uncoupling oxidative phosphorylation

PROPRANOLOL	
Action	Inhibits the peripheral effects of thyroid hormone Beta-blocker. Limits B-adrenergic activity and block peripheral conversion of T4 to T3. Highly lipid soluble, crosses the blood brain barrier so may help with neurologic symptoms
Indications	Tachycardia, hypertension, agitation
Dose	0.5 – 1 mg IV over 10 minutes then 1-2 mg every few hours Adolescent/Adult: 60-80 mg PO every 4-6 hours Infants/Children: 0.5 to 2 mg/kg/day PO divided Q6 hours
Contraindications	Congestive heart failure, hypotension Asthma: choose a cardio-selective agent e.g. Atenolol, Metoprolol Severe asthma: consider rate control with calcium channel blocker
Alternatives	Esmolol: Loading 250-500 mcg/kg then 100 mcg/min infusion
Adverse effects	Hypotension, hypoglycemia, bronchospasm, heart block

THIONAMIDES (Propylthiouracil (PTU), Methimazole). Decreases synthesis of thyroid hormones within 1-2 hours by inhibiting iodine oxidation. Does not effect release of preformed hormone. One or the other is administered and not both. PTU preferred in life-threatening illness. Methimazole for less severe illness (see indications below).

PROPYLTHIOURACIL (PTU)	
Action	Decreases synthesis of thyroid hormones within 1-2 hours Decreases peripheral conversion of T4 to T3
Indications	Preferred for life-threatening illness: Decreases synthesis of thyroid hormones within 1-2 hours, may more rapidly decrease T3 Preferred during first trimester in pregnancy due to less teratogenicity compared to Methimazole (can cross the placenta)
Dose	Adolescent/Adult: 500-1000 mg then 250 mg PO Q4 hours Child: 5-7 mg/day PO divided Q8 hours (maximum 1,200 mg/day)
Adverse effects	Risk of hepatotoxicity with liver failure in 1 of 2,000-4,000 children Reports of fulminant hepatic necrosis requiring liver transplant

METHIMAZOLE	
Action	Decreases synthesis of thyroid hormones within 1-2 hours
Indications	Preferred for severe illness: Longer duration of action, less hepatotoxic, ultimately results in euthyroidism faster than PTU Readily crosses placenta and distributes into breast milk, can be used in pregnancy. Safer in children
Dose	Adolescent/Adult: 60-80 mg/day PO/NG divided Q4-6 hours Infants/Children: 0.5 – 0.7 mg/kg/day PO/NG divided Q8 hours
Adverse effects	Adverse effects seen up to 20% of children. Allergic reactions, fever, myalgias, arthralgias, rash, hepatitis, headache Agranulocytosis in 0.3% of adults (unknown risk in children)

OTHER MEDICATIONS

IODINE	
Action	Blocks synthesis and release of T4 and T3
Indications	At least 1 hour after synthesis blockade with PTU or Methimazole
Dose	Lugol solution: 5% Iodine and 10% Potassium Iodide (126 mg Iodine/ml or 8 mg Iodine per drop) Children/Adolescents: 10 drops PO TID
	SSKI (Saturated Solution of Potassium Iodide (38 mg Iodine/drop) Infants < 1 year: 150-200 mg PO TID Children/Adolescents: 300 to 500 mg PO (5 drops) Q6 hours) Adults: 5 drops (0.25 ml or 250 mg) PO Q6 hours
Contraindications	Do not administer until 1 hour after the dose of thionamide If given prior to synthesis blockade the addition of iodine will act as a substrate promoting further hormone production

GLUCOCORTICOIDS	
Action	Inhibit thyroid hormone release from the thyroid and decreases peripheral conversion of T4 to T3 Decrease autoimmune process in Grave's disease
Indications	Used in extreme cases; patient with CHF, arrhythmias, or shock.
Dose	Dexamethasone 0.2 mg/kg (1-2 mg Q6 hours) or Hydrocortisone (adolescent/adult): 300 mg IV, then 100 mg Q8H Hydrocortisone (infant/child): 1-2 mg/kg Q8 hours

CHOLESTYRAMINE	
Action	Thyroid hormones are metabolized in the liver, get secreted into bile and get reabsorbed if not bound by enterohepatic circulation. Bile acid sequestrants interfere with enterohepatic circulation and reduce thyroid hormone levels
Dose	Adult: 4 grams PO QID