Project: Ghana Emergency Medicine Collaborative

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NON-DIABETIC ENDOCRINE EMERGENCIES
WHY?

- Uncommon, but...
- Potentially lethal
- Diagnostic dilemmas
- ED treatment may be life-saving

Diagram:

1. Hypothalamus
2. CRF
3. Pituitary
4. ACTH
5. Adrenal
6. Cortisol
7. Aldosterone

Feedback:
- Neg. Feedback from CRF to Hypothalamus
- Neg. Feedback from ACTH to Pituitary

Author: Lena Carleton, University of Michigan
Objectives

- Background
- What defines thyroid storm, myxedema coma, adrenal crisis?
- What are the main clinical features?
- What investigations are pertinent?
- What is the emergency management?
Hyper/Hypothyroidism, Adrenal insufficiency

- Often chronic, non-specific symptoms
  - Fatigue/weakness/depression
    - difficult to recognize in a typical medical encounter.

- Classic clinical manifestations more easily recognizable with increased severity

- Acute stresses can precipitate life-threatening
  - Management based mostly on clinical judgment
Case I

- 45 yo female
- “Racing Heart” x48 hr
- Chest Pain
- Breathlessness
- Recent weight loss
- Normal appetite

- Temp 39.8°C
- Rapid Speech/Perseveration
- Tremulous

Jonathan Trobe, M.D., University of Michigan Kellogg Eye Center, [Wikimedia Commons](https://commons.wikimedia.org/wiki/File:Uveitis.jpg)
Definitions

- **Hyperthyroidism**
  - Conditions with ↑thyroid hormone synthesis

- **Thyrotoxicosis**
  - Defined as any state in which thyroid hormone levels are increased in the blood
    - Overproduction (Graves’ disease, toxic multinodular goiter [TMG])
    - Thyroid hormone release from an injured gland (thyroiditis)
    - Exogenous thyroid hormone.
Prevalence of Hyperthyroidism is 0.5-2.2%

- More than 50% of patients considered subclinical
  - Pre-hyperthyroid state
    - depressed thyroid-stimulating hormone [TSH] and normal free $T_4$ (tetra-iodo thyronine, thyroxine)
  - Prevalence in women tenfold > men
Thyroid system

Hypothalamus

Anterior pituitary gland

Thyrotropin-releasing hormone (TRH)

Negative feedback

Thyroid-stimulating hormone (TSH)

Thyroid gland

Thyroid hormones (T3 and T4)

Increased metabolism

Growth and development

Increased catecholamine effect

Mikael Häggström, Wikimedia Commons
Biosynthesis

- **Follicular Cells**
  - Thyroglobulin = large hormonal precursor protein with numerous tyrosines
  - Iodine actively transported into follicular cells and oxidized/bound to tyrosine residues.
    - Iodo-tyrosines + thyroglobulin $\rightarrow T_4$ and $T_3$
      - released into the circulation by proteolyisis.
  - All $T_4$ produced in thyroid gland
  - 15-20% of $T_3$ is synthesized directly
    - Remainder via de-iodonation of $T_4$ in peripheral tissues.
Graves Disease

- Most common cause of thyrotoxicosis

  - Hyperthyroidism, diffuse symmetrical goiter, ophthalmopathy, and dermopathy.

  - Primarily affects females 20-40 years
    - often those with a family history of thyroid disease.

- Autoimmune Disorder
  - B lymphocytes produce immunoglobulins that stimulate the TSH receptor (thyroid-stimulating immunoglobulin [TSI]).
  - Eye disease thought to result from thyroid antibodies sensitized to common antigens in orbital fibroblasts and muscle.
$T_3$ and $T_4$ increase the number and sensitivity of beta-adrenergic receptors, dramatically increasing response to endogenous catecholamines.
Toxic Multinodular Goiter (TMG)

2nd leading cause of hyperthyroidism

- Multiple autonomously functioning nodules
  - women >50 years of age, iodine-deficient

- Iodine deficient populations
  - Central Africa, Central/South America, Himalayas, E. Europe

- Sx milder than Graves’ disease, gradual in onset
  - Iodine replacement given to an iodine-deficient individual (Jod-Basedow effect) → **acute presentation due to ↑substrate**
  - Due to age → atrial fibrillation and CHF common
    - Tremors and hyper-metabolic features are less severe
    - Muscle wasting and weakness common ≈ “Apathetic”
Thyroid Storm Pathophysiology

- **Acute stress** → surge of catecholamines
  - e.g., glycogenolysis and catecholamine-mediated antagonism of insulin → hyperglycemia
  - ↑ free $T_4/T_3$ → ↑ catecholamine-binding sites

Heightened response to adrenergic stimuli
Thyroid Storm Diagnosis
Criteria

- Exaggeration of the clinical manifestations of thyrotoxicosis, further distinguished by the presence of fever, marked tachycardia, central nervous system dysfunction, and gastrointestinal symptoms.

- Decompensation of one or more organ systems, such as shock or heart failure.
Patient Complaints in Thyrotoxicosis

- Retraction of the upper/lower eyelids revealing a rim of sclera beyond the limbus.

- Eyelids are sympathetically innervated so ↑ sensitivity to adrenergic stimuli in thyrotoxicosis leads to widening of the palpebral fissures

- Constitutional: Weight loss despite hyperphagia, fatigue, generalized weakness
- Hypermetabolic: Heat intolerance, cold preference, excessive perspiration
- Cardiorespiratory: Heart pounding and racing, dyspnea on exertion, chest pains
- Psychiatric: Anxiety, restlessness, hyperkinesis, emotional lability, confusion
- Muscular: Tremor, difficulty getting out of a chair or combing hair
- Ophthalmologic: Tearing, irritation, wind sensitivity, diplopia, foreign body sensation
- Thyroid Gland: Neck fullness, dysphagia, dysphonia
- Dermatologic: Flushed feeling, hair loss, pretibial swelling
- Reproductive: Oligomenorrhea, decreased libido, gynecomastia
Etiology of Thyroid Storm

Undiagnosed vs. Undertreated

Acute Precipitant

Thyroid Storm

- 1 - 2% of patients with thyrotoxicosis will progress on to thyroid storm in the setting of an acute stressor

- 20% mortality
Causes of Thyrotoxicosis

Graves’ disease (toxic diffuse goiter)
Toxic multinodular goiter
Toxic adenoma (single hot nodule)
Factitious thyrotoxicosis
Thyrotoxicosis associated with thyroiditis
  Hashimoto’s thyroiditis
  Subacute (de Quervain’s) thyroiditis
Postpartum thyroiditis
Sporadic thyroiditis
Amiodarone thyroiditis

Iodine-induced hyperthyroidism (areas of iodine deficiency)
  Amiodarone
  Radiocontrast media
Metastatic follicular thyroid carcinoma
hCG-mediated thyrotoxicosis
  Hydatidiform mole
  Metastatic choriocarcinoma
  Hyperemesis gravidarum
TSH-producing pituitary tumors
Struma ovarii

hCG, human chorionic gonadotropin;
TSH, thyroid-stimulating hormone
Precipitants of Thyroid Storm

Medical
- Infection/sepsis
- Cerebral vascular accident
- Myocardial infarction
- Congestive heart failure
- Pulmonary embolism
- Visceral infarction
- Emotional stress
- Acute manic crisis

Endocrine
- Hypoglycemia
- Diabetic ketoacidosis
- Hyperosmolar nonketotic coma

Trauma
- Thyroid surgery
- Nonthyroid surgery
- Blunt and penetrating trauma to the thyroid gland
- Vigorous palpation of the thyroid gland
- Burns

Drug-Related
- Iodine-131 therapy
- Premature withdrawal of antithyroid therapy
- Ingestion of thyroid hormone
- Iodinated contrast agents
- Amiodarone therapy
- Anesthesia induction
- Miscellaneous drugs (chemotherapy, pseudoephedrine, organophosphates, aspirin

Pregnancy-Related
- Toxemia of pregnancy
- Hyperemesis gravidarum
- Parturition and the immediate postpartum period
Disease Progression

- Underlying Hyperthyroidism
  - Weight loss, heat intolerance, tremors, anxiety, diarrhea, palpitations, sweating, CP, SOB, goiter, eye findings, pre-tibial myxedema *(non-pitting edema assoc with fibroblast activation → increase synthesis of glycosaminoglycans)*

- Fever
  - Expected physiological vasodilation for heat dissipation lost as system is already vasodilated due to “running hot”

- Altered Mental Status (Metabolic Encephalopathy)
  - Mild impairment → psychosis → frank coma
**The Elderly: Difficult to Diagnose**
- Fewer overt signs of hyperthyroidism
  - Cell surface $\beta$ receptors internalized with age
- **Clues:** SVT/arrhythmia, new heart failure

**The Young: Difficult to Treat**
- Poor toleration of state vs elderly
  - Relatively higher number of surface $\beta$ receptors leads to exaggerated adrenergic response
  - More likely to die from circulatory collapse
**Apathetic Hyperthyroidism**

- Usually Elderly *(but can be any age)*
- New onset Altered LOC, Afib, CHF, Angina
- Minimal fever/tachycardia
- No preceding hx of hyperthyroidism except weight loss
- More common than thyroid storm
- Check TSH in any elderly patient with
  - Altered LOC, new psychiatric presentation, Atrial Fibrillation, CHF
INVESTIGATIONS

- **Thyroid Testing**
  - TSH
  - Free T₄

- **Look for precipitant**
  - ECG
  - CXR
  - Urine
  - Labs
  - Blood cultures
  - Tox screen
  - ? CT head
  - ? CSF
Thyroid Storm: Goals of Management

1 - Decrease Hormone Synthesis/Release
2 – Decrease Adrenergic Symptoms
3 - Decrease Peripheral $T_4 \rightarrow T_3$
4 - Supportive Care
Decrease Hormonal Synthesis

- Inhibition of thyroid peroxidase

- Propylthiouracil (PTU) *(or Methimazole)*
  - PTU 600-1000 mg PO/NG/PR then 250mg q4hr
  - No IV form
  - Pregnancy Risk – category D
    - Evidence of fetal harm, consider fetal risk-maternal benefit
    - Lactation Safe
  - Adverse Rxn: rash, SJS, BM suppression, hepatotoxic
  - Contraindications: previous hepatic failure or agranulocytosis from PTU
  - *Alternative:* Methimazole dose: 20-25mg PO x1 then q4hr
  - **NOTE:** Phenytoin, Phenobarbitol enhance T₄ metabolism
Decrease Hormone Release

- Iodine further decreases release cell storage
  - Given ≥ 1hr after PTU
    - iodine load presented to an actively synthesizing gland provides further substrate for hormone

- Potassium Iodide 5 drops PO/NG/PR q6hr

- Or Lugol’s solution 8 drops q6hr

- Or Li⁺ 300 mg every 6 hours PO/NG
  - Levels monitored to maintain a level of ≈ 1 mg/ L.
Mechanism

- Excess Iodide
  - Inhibits iodide trapping and thyroglobulin iodination (the Wolff-Chaikoff effect)
    - Autoregulatory phenomenon that inhibits oxidation of iodide in the thyroid gland, formation of thyroid hormone within follicle cells and the release of thyroid hormone into the bloodstream
  - Blocks release of thyroid hormone from the gland.
    - Inhibition of thyroid hormone production and release is transient, with the gland escaping inhibition after 10 to 14 days
      - "Escape phenomenon" is believed to occur because of decreased inorganic iodine concentration secondary to down-regulation of Na⁺-I⁺ Symporter in the baso-lateral membrane of follicular cells
Caution

- Iodide load can induce hyperthyroidism (Jod-Basedow effect) in some patients with multinodular goiter and latent Graves’ disease, especially if the patient is iodine-deficient to begin with.
Adrenergic Blockade

- **Cover for Infection if suspected**
  - Impaired immune response
    - broad-spectrum antibiotics for elevated WBC count, Blood Cx

- **Symptomatic Relief (Arrythmia, Tachycardia)**
  - Propranolol 1 mg IV ($t_{1/2}$ 5 min) over 10min
    - then q10-15min prn as tolerated
    - Some $T_4 \rightarrow T_3$ plus non-selective effects to improve tachycardia, tremor, hyperpyrexia, and restlessnes
    - PO 120-240mg qD if BP stable, otherwise IVF + observe
    - Reserpine if β blocker contraindicated
Steroids

- Some Inhibition of $T_4 \rightarrow T_3$ conversion
  - Hydrocortisone 300mg IV then 100mg q6hr
  - Or Dexamethasone 2 – 4 mg IV q6hr
  - PTU and propranolol also have some effect

- Treats relative adrenal insufficiency
Supportive/Additional Care

- Fluid rehydration
  - Normal saline → D5/0.9NS due to depletion of glycogen stores
- Correct electrolyte abnormalities
- Search for precipitant
- Congestive Heart Failure
  - Primarily high output → β blockers
  - Diuretics not first line given hypovolemia
Temperature Control

Temperature Regulation

- Cool mist, ice packs, fans
- Acetaminophen
  - ✓ AST/ALT given possible liver compromise
- Aspirin contraindicated because it increases levels of free thyroid hormone

Risks of Aggressive Cooling

- Peripheral vasoconstriction and paroxysmal hyperthermia
- Some use of agents that act on hypothalamic heat regulation
  - Demerol 25mg IV, Thorazine 25mg IV
Summary of Management

- PTU
- PROPRANOLOL
- POTASSIUM IODIDE
- STEROIDS
- SUPPORTIVE CARE

*synergistic effect of PTU, iodide, and steroids in thyrotoxicosis can restore the concentration of $T_3$ to normal within 24 to 48 hours*
Management of Thyroid Storm

Inhibition of Thyroid Hormone Synthesis
Propylthiouracil 600-1000 mg loading dose, then 200-250 mg every 4 hr
OR
Methimazole 20-25 mg initially, then 20-25 mg every 4 hr (Preferred route: PO or NG. Alternative route: PR. Enema prepared by pharmacy. Same dose for all routes. No IV preparation is available, but IV methimazole can be prepared with the use of a Millipore filter and given 30 mg every 6 hr)

Inhibition of Thyroid Hormone Release
Saturated solution of potassium iodide (SSKI) 5 gtt by mouth, NG, or PR every 6 hr
OR
Lugol’s solution 8 gtt by mouth, NG, or PR every 6 hr
OR
Sodium iodide 500 mg in solution prepared by pharmacy IV every 12 hr
OR
If allergic to iodine, lithium carbonate 300 mg by mouth or NG every 6 hr

Beta-adrenergic Blockade
Propanolol 60-80 mg PO every 6 hr
OR
Metoprolol 50 mg PO every 6 to 12 hr
If IV route required, propanolol 0.5-1.0 mg IV slow push test dose, then repeat every 15 min to desired effect, then 2-3 mg every 3 hr
OR
Esmolol 250-500 µg/kg bolus, then 50-100 µg/kg/min infusion
Strict contraindication to beta-blocker: resperine 0.5 mg PO every 6 hr

Administration of Corticoestrogens (inhibit T₄ to T₃ conversion, treat relative adrenal insufficiency)
Hydrocortisone 300 mg IV, followed by 100 mg every 6 hr
OR
Dexamethasone 2-4 mg IV every 6 hr

Diagnosis and Treatment of Underlying Precipitant
Consider empirical antibiotics if critical

Supportive Measures
Volume resuscitation and replacement of glycogen stores
D/0.9NS 125-1000 mL/hr depending on volume status and CHF
Tylenol with caution
Cooling blanket, fans, ice packs, ice lavage

Miscellaneous
Lorazepam or diazepam as anxiolytic and to decrease central sympathetic outflow
L-Carnitine (block entry of thyroid hormone into cells), 1 g PO every 12 hr
Cholestyramine (block enterohepatic recirculation of thyroid hormone), 4 g PO every 6 hr

CHF, congestive heart failure; D/0.9NS, 5% dextrose in 0.9% normal saline; IV, intravenous; NG, nasogastric; PO, by mouth; PR, in rectum; T₃, triiodothyronine; T₄, thyroxine
Pearls and Conclusions

- Should improve overall within 18-24 hours, with mental status improvement in a few hours

- On average, require 3-5L IVF (cautiously)

- Atrial Fibrillation $\rightarrow$ most convert via $\beta$ blocker
  - Digoxin: increased clearance = higher dosing needed
    - Short Term: risk of SMA spasm $\rightarrow$ mesenteric ischemia
    - Long Term: digoxin toxicity associated with higher doses
  - Calcium Channel Blockers: Do not decrease heart work
  - Anticoagulation: decreased embolism risk no CHF
Thyrotoxicosis and Thyroid Storm: Special Situations

**Congestive Heart Failure**
If rate-related, high-output failure
Beta-blockage is first-line therapy
ACEI, digoxin, diuretics as needed
If depressed EF
Avoid beta-blocker or ¼ dose
ACEI if BP adequate
Digoxin and furosemide as needed
If pulmonary hypertension
Oxygen
Sildenafil

**Atrial Fibrillation**
Beta-blocker preferred for rate control
Calcium channel blockers prone to hypotension;
diltiazem 10-mg test dose. Avoid verapamil
Digoxin less effective but may be tried
Amiodarone should be avoided due to iodine load
Refractory to conversion to sinus unless euthyroid first

**Thyroiditis (Subacute)**
NSAIDs for inflammation and pain control
Prednisone 40 mg/day if refractory to NSAIDs
Beta-blockade to control thyrotoxic symptoms
No role for PTU, methimazole, or iodides

**Factitious Thyrotoxicosis**
Beta-blockade for thyrotoxic symptoms
Cholestyramine to block absorption of ingested thyroid hormone
No role for PTU, methimazole, or iodides

**ACEI**, angiotensin-converting enzyme inhibitor; **BP**, blood pressure; **EF**, ejection fraction; **NSAIDs**, nonsteroidal anti-inflammatory drugs; **PTU**, propylthiouracil
Case II

- 36 year old female with history of non insulin-dependent diabetes presents to A&E with altered mental status. Family reports that she is “always cold,” weak and often complains of “brittle” hair. She is said to steadily gaining weight despite no change in food intake and has had a productive cough x 2 weeks with intermittent fever.

- VS: HR 67, RR 5, temp 35 C, O2 82% RA
Hypothyroidism

- Prevalence of TSH elevation
  - Ranged from 3.7-9.5%, with the majority of these having a normal free $T_4$ (subclinical).
  - Overt hypothyroidism ($\uparrow$TSH, $\downarrow$free $T_4$) is seen in a minority
    - 0.3% of the population overall, with the prevalence rising with age, such that patients older than 80 years have a fivefold greater likelihood of developing hypothyroidism than do 12 to 49-year-olds.
Etiologies

- **Hashimoto’s Thyroiditis**
  - Thyroid gland failure caused by autoimmune destruction of the gland

- **Goiter**
  - In younger patients, elevated anti-thyroid antibodies, specifically to thyroid peroxidase, thyroglobulin, and TSH.
  - TSH receptor antibody in Hashimoto’s disease blocks the receptor
    - in contrast to the stimulating antibody in Graves’ disease
End-stage Graves’ Disease (Hyper → Hypo)

- Autoimmune destruction of the thyroid gland following several exacerbations of hyperthyroidism.
- Following treatment of Graves’ disease with radioactive iodine or thyroidectomy

Thyroidectomy
Drug-induced hypothyroidism

- Li₂CO₃ = inhibits hormone release.
- Iodine excess
  - amiodarone, iodinated contrast media, kelp supplements, and iodine-containing cough medicines
    - impair thyroid hormone release and synthesis (Wolff-Chaikoff effect), thereby converting subclinical hypothyroidism to overt hypothyroidism and sometimes precipitating hypothyroidism de novo
Causes of Hypothyroidism

Primary Hypothyroidism

Autoimmune hypothyroidism
- Hashimoto’s thyroiditis (chronic – atrophic thyroid, acute with goiter)
- Graves’ disease (end stage)

Iatrogenic
- Radioactive iodine therapy for Graves’ disease
- Thyroidectomy for Graves’ disease, nodular goiter, or thyroid cancer
- External neck irradiation for lymphoma or head and neck cancer

Iodine-related
- Iodine deficiency (common worldwide, but rare in North America)
- Iodine excess (inhibition of hormone release can unmask autoimmune thyroid disease) (see under Drug-related)

Drug-related
- Lithium (inhibit hormone release)
- Amiodarone (destructive thyroiditis or iodine excess)
- Interferon-alfa (precipitate Hashimoto’s thyroiditis)
- Iodine excess (iodinated contrast media, kelp, amiodarone)
- Propylthiouracil, methimazole
- Interference with thyroid hormone absorption in patients on replacement therapy (iron, calcium, chromium, phosphate binders, cholestyramine, colestipol)

Thyroiditis
- Subacute
- Silent (sporadic)
- Postpartum
- Amiodarone

Congenital defect in thyroid hormone synthesis

Central Hypothyroidism

Euthyroid sick syndrome
Pituitary disease
- Pituitary adenoma
- Hemorrhage
- Infiltrative (amyloid, sarcoid)
Hypothalamic disease
Myxedema Coma
Decompensated Hypothyroidism with Vascular Collapse

- ↓ metabolic rate → decreased body temp → vasoconstriction

Physical Exam
- Appear older than stated age, cool to touch, dry skin, mild HTN, altered mental status, hypothermia (commonly<32 C)
- Swelling of hands, face, feet, periorbital tissues accumulation of glycosaminoglycans in interstitial fluids associated with capillary leak.
- Delayed deep tendon relaxation

Precipitant → Acute Decompensation
- Infection → vasodilation → vascular collapse
  - Hemodynamics: reduced cardiac output/blood volume
Etiology of Myxedema Coma

Undiagnosed
Undertreated
(Hashimoto’s thyroiditis, post surgery/ablation most common)

Acute Precipitant

Myxedema Coma
Myxedema Coma

Precipitants of Myxedema Coma

- Infection (esp. Pneumonia)
- Trauma
- Vascular: CVA, MI, PE
- Noncompliance with Rx
- Any acute medical illness
- Cold
Myxedema Coma: Aggravating or Precipitating Factors

Infection/sepsis (especially pneumonia)
Exposure to cold
Cerebrovascular accident
Drug effect
  *Altered sensorium*: Sedative-hypnotics, narcotics, anesthesia, neuroleptics
  Decrease $T_4$ and $T_3$ release: amiodarone, lithium, iodides
  Enhance elimination of $T_4$ and $T_3$: phenytoin, rifampin
  *Inadequate thyroid hormone replacement*: noncompliance; interference with absorption
  (iron, calcium, cholestyramine)
Myocardial infarction
Gastrointestinal bleeding
Trauma/burns
Congestive heart failure
Hypoxia
Hypercapnia
Hyponatremia
Hypoglycemia
Hypercalcemia
Diabetic ketoacidosis

$T_3$, triiodothyronine; $T_4$, thyroxine
Recognition of Myxedema Coma

Patient profile: Elderly female in the winter
Known hypothyroidism; thyroidectomy scar
Hypothermia: Usually below 95.9°F; below 90°F is bad prognostic sign; as low as 75°F reported. Near normal in presence of infection
Altered mental status: Lethargy and confusion to stupor and coma, agitation, psychosis and seizures (myxedema madness)
Hypotension: Refractory to volume resuscitation and pressors unless thyroid hormone administered
Slow, shallow respirations with hypercapnea and hypoxia; high risk of respiratory failure
Braxycardia (sinus)/long QT and ventricular arrhythmias
Myxedema facies: Puffy eyelids and lips, large tongue, broad nose
Evidence of severe chronic hypothyroidism: Skin, hair, reflexes, bradykinesia, voice
Acute precipitating illness (e.g., pneumonia)
Drug toxicity (e.g., sedative, narcotic, neuroleptic)
Hyponatremia
## Symptoms and Signs of Hypothyroidism

**Vital Signs**
- Systolic BP—normal or low
- Diastolic BP—normal or elevated
- Slow pulse to sinus bradycardia
- Respirations—normal or slow, shallow
- Temperature—normal, but prone to hypothermia with stress

**Hypometabolic Complaints**
- Cold intolerance
- Fatigue
- Weight gain, but decreased appetite

**Cutaneous**
- Coarse, brittle hair
- Alopecia
- Dry skin, decreased perspiration
- Pallor, cool hands and feet
- Coarse, rough skin
- Yellow tinge from carotenemia
- Thin, brittle nails
- Lateral thinning of the eyebrows

**Neurologic**
- Slow mentation and speech
- Impaired concentrating ability and attention span
- Lethargy
- Decreased short-term memory
- Agitation, psychosis
- Seizures
- Ataxia, dysmetria
- Mononeuropathy
  - Carpal tunnel syndrome
  - Sensorineural hearing loss
- Peripheral neuropathy

**Muscular**
- Proximal myopathy
- Pseudohypertrophy
- Delayed relaxation of reflexes (hung-up or pseudomyotonic)

**Cardiac**
- Decreased exercise capacity
- Dyspnea on exertion

**Sinus bradycardia**
- Long QT with increased ventricular arrhythmia
- Chest pain—accelerated coronary disease
- Diastolic heart failure (delayed ventricular relaxation)
- Pericardial effusion (asymptomatic)
- Peripheral edema

**Respiratory**
- Dyspnea on exertion
- Obstructive sleep apnea
- Primary pulmonary hypertension

**Gastrointestinal**
- Constipation
- Ileus
- Gastric atrophy

**Reproductive**
- Oligo- and amenorrhea
- Menorrhagia
- Decreased fertility
- Early abortions
- Decreased libido
- Erectile dysfunction

**Rheumatic**
- Polyarthralgias
- Joint effusions
- Acute gout or pseudogout

**HEENT**
- Hoarseness
- Deep, husky voice
- Macroglossia
- Hearing loss
- Periorbital swelling
- Broad nose
- Swollen lips
- Goiter

BP, blood pressure; HEENT, head, ear, eyes, nose, and throat.

Source Undetermined
Clinical Diagnosis

- **Hyponatremia**
  - Elevated levels of antidiuretic hormone and/or diminished blood flow to the kidneys secondary to decreased cardiac output thought responsible for the inability to excrete free water

- **Hypoglycemia**
  - Result of down-regulation of metabolism seen in hypothyroidism
  - May also indicate the possibility of adrenal insufficiency

- **Delayed return of deep tendon reflexes**

- **Hypothermia**

- **Altered mental status**
  - Multifactorial
    - Thyroid hormone deficiency, hypothermia, hypercapnea, hyponatremia, hypotension, and hypoglycemia

- **Precipitating Event (infection)**
Laboratory Testing

- **Investigations**
  - TSH and Free $T_4$
  - Cortisol level
    - Prior to giving $T_4$
      - **Risk of Schmidt’s Syndrome** – autoimmune destruction of BOTH adrenals/thyroid glands

- **Look for precipitant**
  - ECG
  - Labs
  - Septic work up (CXR/BCx/urine/ +/- LP)
    - But both temp and WBC are low... Think Gram Negative
  - CT head?
Management

- **Treatment**
  - airway management, fluid resuscitation, thyroid hormone replacement, general supportive measures, and treatment of the precipitating illness

- $T_4$ 500mcg IVP
  - **Even if TSH unknown, acute effects mitigated by:**
    - Illness: even slower $T_4 \rightarrow T_3$ (active form) conversion
    - Binding Proteins: majority of $T_4$ not available
    - Peaks in 2 weeks (vs $T_3$ in 24 hr) – $T_3$ can overwhelm heart
    - 1st physical sign of efficacy = ▲ HR at 12 hr mark

  - **Alternative to rapidly correct young critically ill patients**
    - $T_3$ 10-20mcg IV then 10mcg IV q4hr x24 hr
    - Then 10mcg IV q6hr x 1-2 days
**Hydrocortisone** *(prior to giving $T_4$)*

- ↑ metabolism after thyroxine administration can deplete cortisol stores → adrenal insufficiency
- Central hypothyroidism with ACTH deficiency
- Schmidt Syndrome
  - Autoimmune destruction of both thyroid and adrenal glands
- Relative Adrenal Insufficiency
  - unmasked by stress and the enhanced clearance of cortisol.
- Hydrocortisone 50-100 mg IV q6-8 hr
Other Management

- **Airway**
  - May be partial obstruction from macroglossia and supraglottic edema, myopathy of respiratory muscles, and central hypoventilation.
  - Most require endotracheal intubation and prolonged ventilatory support.
    - **ABG predictions?**
      - RR 5 breaths/min vs 55 breaths/min (less common)
    - **Appropriate ventilator settings?**
• Fluids for Hypotension
  ○ Intravascular volume depletion even with normal vital signs.
  ○ Aggressiveness of administration should tempered by the risk of unmasking CHF.
  ○ Initial fluid of choice D5/ 0.9NS because the myxedema coma patient is at high risk for both hyponatremia and hypoglycemia

• Hypothermia
  ○ Passive Re-warming using regular blankets and prevention of further heat loss.
    • risk that the resulting vasodilation will lead to a fall in peripheral vascular resistance and hypotension.
    • Avoid excessive mechanical stimulation due to risk of precipitating arrhythmias.
TREATMENT OF MYXEDEMA COMA

Protect the airway/ventilatory support; monitor for alkalosis

Fluid resuscitation:
  0.9NS or D₂/0.9NS if hypoglycemia
  Watch for unmasking of CHF

Thyroid hormone replacement:
  T₄ alone (elderly and patients with cardiac comorbidity):
    T₄ 300–500 µg IV as initial bolus
    Or split bolus 200–300 µg IV day 1 and 2
    Then 50–100 µg IV daily until able to take PO
  T₃ alone (younger patient, no cardiac risks; rapid correction desired):
    T₃ 10–20 µg IV initially, then 10 µg IV every 4 hr for 1 day, then 10 µg IV every 6 hr for 1–2 days
  Combination T₄ and T₃ therapy (intermediate approach):
    T₄ 200–250 µg IV as initial bolus
    T₃ 10 µg IV initial dose, then 10 µg IV every 8–12 hr
    T₃ 100 µg IV in 24 hr, followed by 50 µg/day

Hydrocortisone
  50–100 mg IV every 6–8 hr

Hyponatremia
  Avoid hypotonic fluids, use only 0.9NS or D₂/0.9NS
  If less than 120 mEq/L, consider 3% saline, 50–100 mL boluses

Passive rewarming
  Regular blankets, prevent heat loss
  If heating blankets considered, pretreat with IV fluids and monitor BP closely
  Avoid mechanical stimulation
  Treatment of any precipitating illness, with special attention to infectious causes

BP: blood pressure; CHF: congestive heart failure; D₂/0.9NS: 5% dextrose in 0.9% normal saline; IV: intravenous; T₃: triiodothyronine; T₄: thyroxine.
Outcomes

- Without thyroid hormone replacement and a vigorous approach, the mortality rate from myxedema coma exceeds 80%.
- With rapid treatment and ICU care, rate falls to ≤ 20%.
- Factors that predict a poor outcome:
  - advanced age, body temperature < 32°C, hypothermia refractory to treatment, hypotension, pulse < 44 beats per minute and sepsis.
Common Mistakes

- Not considering hypothyroidism
- Active re-warming rather than passive
- Not treating infection
- Treating Hypotension with Vasopressors
  - Paradoxical worsening of hypotension $\rightarrow$ IVF
- If not better in 24 hours look for alternative etiology (e.g., meningitis)
Case III

- 58 year old female with history of asthma, emphysema and mild heart failure who takes methylprednisolone qDay presents with altered mental status, fever, tachycardia, tachypnea and reproducible BP 60/30

- Transferred from an outside hospital

- Family reports that she increased her dose herself last month because it makes her feel better given that she has been coughing and wheezing. They don’t know how many pills she takes a day or when her last dose was but her bottle is empty sooner that it should be.

- Fever breaks after acetaminophen, labs/radiology pending, but patient remains hypotensive despite 5L NS.

- Adrenaline infusion is then started but there is continued refractory hypotension with BP 65/40
1300 hours at the Previous Hospital
1345 hours (On Arrival ➔ Time to Treat)
Adrenal Insufficiency

Lena Carleton, University of Michigan
Key Etiologies

- **Primary = Adrenal Gland Destruction**
  - **Addison’s Disease**
    - West = autoimmune adrenalitis
    - Globally = destruction by tuberculosis
  - **Disseminated Infection:**
    - blastomycosis, CMV, toxoplasmosis, histoplasmosis, *Mycobacterium avium*, *Pneumocystis* (primarily assoc with AIDS)
  - **Infiltrative:**
    - Kaposi’s Sarcoma (20% critical AIDS patients → cortisol deficiency)
  - **Cancer:**
    - most commonly metastases from lung and breast cancer
    - Idiopathic, infarction/hemorrhage, post-operative, congenital adrenal hypoplasia (Peds), Drugs (etomidate infusion > RSI dose)
Secondary = Pituitary failure (no ACTH)

- Responsiveness/atrophy with Chronic Glucocorticoid use
  - Generally >3 weeks, but as little as 5 days
  - > than q Day and any evening dosing have greater suppressive effect on pituitary ACTH production

- Pituitary Apoplexy
  - Hemorrhage into a pituitary adenoma
  - Sx: Hypotension, sudden severe headache, diplopia, visual field cuts

- Sheehan Syndrome
  - Post-partum hypotension → ischemic necrosis of the pituitary

- Traumatic Brain Injury
  - 13% of patients with GCS 3-13 developed ACTH-deficiency
Functional

- Critically ill patients with inability to mount an adequate ACTH and cortisol response to sepsis or overwhelming stress → increased mortality

- >50% of patients with septic shock have some degree of relative adrenal insufficiency

- Associated With:
  - Sepsis, hepatic failure, severe acute pancreatitis, trauma
## BOX 126-12 CAUSES OF ADRENAL INSUFFICIENCY

### Primary Adrenal Insufficiency

**Chronic**
- Autoimmune adrenalitis (Addison’s disease)—isolated or polyglandular deficiency, HIV infection (direct involvement or disseminated CMV, MAI, TB, cryptococcosis, histoplasmosis, blastomycosis, toxoplasmosis, *Pneumocystis* pneumonia)
- TB and disseminated infections as seen with HIV
- Metastatic cancer (breast, lung)
- Infiltrative (sarcoid, hemochromatosis, amyloid)
- Congenital (adrenal hypoplasia, adenoleukodystrophy, ACTH resistance)
- Bilateral adrenalectomy
- Drug toxicity (etomidate, ketoconazole, rifampicin)

**Acute**
- Adrenal hemorrhage
  - Meningococcemia and other sepsis
  - Anticoagulation (heparins and warfarin)
  - Anticardiolipin antibody syndrome
  - Trauma

### Secondary Adrenal Failure

**Chronic**
- Pituitary tumor (primary or metastatic)
- Pituitary surgery or irradiation
- Chronic steroid use with functional deficiency
- Infiltrative (sarcoid, eosinophilic granuloma, TB)
- Traumatic brain injury
- Postpartum pituitary necrosis (Sheehan’s syndrome)
- Empty sella syndrome

**Acute**
- Pituitary apoplexy (hemorrhage into a pituitary tumor)
- Postpartum pituitary necrosis (Sheehan’s syndrome)
- Traumatic brain injury
- Relative adrenal insufficiency (sepsis, hepatic failure, severe acute pancreatitis, trauma)

ACTH, adrenocorticotropic hormone; CMV, cytomegalovirus; HIV, human immunodeficiency virus; MAI, *Mycobacterium avium-intracellulare*; TB, tuberculosis.
Progression of Adrenal Crisis

Underlying Adrenal Insufficiency
(Addision’s and Chronic Steriods)

Acute Precipitant

Acute destruction vs Chronic Suppression

Acute illness or stress overwhelms the patients limited cortisol reserve
Acute Adrenal Crisis?

- Underlying Adrenal insufficiency
  - Addison’s disease
  - Chronic steroid use
    - Most common
  - Acute illness or stress overwhelms the patients limited cortisol reserve.

- Precipitants
  - Surgery
  - Anesthesia
  - Procedures
  - Infection
  - MI/CVA/PE
  - Alcohol/drugs
  - Hypothermia

No known underlying Adrenal Insufficiency = Infarct/Hemorrhage?
Adrenal Hemorrhage/Infarction

- **Sepsis**
  - Waterhouse-Friderichsen Syndrome (Meningococcal sepsis)
    - Pseudomonas, Escherichia coli, group A Streptococcus, Pneumococcus, Staphylococcus

- **Trauma or surgery**
  - Blunt thoraco-abdominal trauma (liver, spleen, kidney)

- **Coagulopathy**
  - Warfarin/Heparin
    - Excess use or use during severe stress

- **Spontaneous**
  - Antiphospholipid Ab Syndromes (venous infarction), Sheehan Syndrome, Apoplexy
Key Features of Adrenal Crisis

- **Sx Vague/Nonspecific**
- **Psychiatric (Early)**
  - Depression, apathy, memory impairment → confusion, delirium, dementia-like picture, and psychosis

- **Refractory Shock**
  - Unresponsive to fluids/pressors
  - Hypotension out of proportion to current illness

- **Laboratory**
  - $\downarrow Na^+$, $\uparrow K^+$
  - metabolic acidosis ($\uparrow H^+$)

- **Known Adrenal insufficiency?**
- **Undiagnosed adrenal insufficiency?**
  - Persistent weakness, fatigue, weight loss, anorexia, N/V, abdominal pain, salt craving, postural hypotension
  - Hyperpigmentation
    - sun-exposed areas
    - palmar creases, nipples, axillae, recent scars, and all mucous membranes
## Clinical Features of Adrenal Insufficiency

### General
- Weakness, fatigue: 100%
- Anorexia: 100%
- Gastrointestinal symptoms: 92%
- Weight loss: 100%
- Hyponatremia: 90%
- Blood pressure $\leq 110/70$ mm Hg: 88–94%
- Fevers (mild): Common
- Depression, apathy: 20–40%
- Myalgia, arthralgias: 6–13%
- Auricular calcifications: 5%

### Primary
- Hyperpigmentation: 94–97%
- Salt craving: 16–22%
- Orthostasis, syncope: 12–16%
- Vitiligo: 10%
- Hyperkalemia: 65%
- Hyperchloremia and acidosis: 65%
- Hypoglycemia: Mild, occasional

### Secondary
- Hyperkalemia: Not present
- Hyperpigmentation: Not present
- Hypoglycemia: More severe, common
- Orthostasis, hypotension: Uncommon
- Amenorrhea: Common
- Axillary and pubic hair loss: Occasional
- Decreased libido: Occasional

### Crisis
- Refractory hypotension: 100%
Hyperpigmentation

Original Image: chris@APL, Flickr
Altered Image: Lena Carleton, University of Michigan

FlatOut, Wikimedia Commons
Hypermelanosis

- **ACTH**
  - Share POMC precursor with melanocyte-stimulating hormone (MSH)
    - POMC cleavage $\rightarrow$ ACTH, $\gamma$-MSH, $\beta$-lipoprotein
    - ACTH subunit further cleavage $\rightarrow$ $\alpha$-MSH (pigments skin)
    - Given $\downarrow$ feedback on Ant Pituitary $\rightarrow$ $\uparrow$ACTH
Investigations

- Adrenal Function
  - ✔ Electrolytes
    - Random cortisol
    - ACTH

- Look for Precipitant
  - ECG
  - CXR
  - Labs
  - Urinalysis
  - ± EtOH/Tox panel
Electrolyte Derangement

- Adrenal gland failure $\rightarrow$ ↓aldosterone, ↓Na$^+$

- Cortisol deficiency $\rightarrow$ ↑ADH $\rightarrow$ ↑Free H$2\text{O}$
  - Although aldosterone is not deficient in secondary adrenal insufficiency, ↑ADH secretion alone results in hyponatremia in about 50% of patients

- Due to aldosterone deficiency, hyperkalemia is seen in about two thirds of patients with primary adrenal insufficiency

- Hyperchloremic Metabolic Acidosis
  - Accompanies the elevated potassium due to impaired exchange of sodium with hydrogen and potassium when aldosterone is deficient
  - *What resuscitation fluid is appropriate here?*
Cosyntropin (ACTH) Stimulation Test

- Random cortisol <20 µg/dL → stimulation test
  - Can be performed any time of the day**
  - Baseline cortisol then 250 µg of ACTH IV bolus
  - Repeat serum cortisol levels at 30 or 60 minutes.
  - Post-ACTH cortisol >20 µg/dL to exclude diagnosis.

- Acutely Ill Patient:
  - **the physiologic stress should result in an elevation of serum cortisol regardless of the time of the day, such that a random level is adequate.
  - cortisol level below 15 µg/dL is presumptive evidence of hypo-adrenalism.
<table>
<thead>
<tr>
<th>Table 126-3</th>
<th>Diagnosis of Hypoadrenal States</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEVEL</strong> (µg/dL)</td>
<td><strong>DIAGNOSTIC CONCLUSION</strong></td>
</tr>
<tr>
<td><strong>Chronic, Nonstressed</strong></td>
<td></td>
</tr>
<tr>
<td>Serum cortisol (6–8 AM)</td>
<td>&lt;3</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
</tr>
<tr>
<td>ACTH stimulation test (peak)</td>
<td>&lt;20</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
</tr>
<tr>
<td><strong>Acute Crisis</strong></td>
<td></td>
</tr>
<tr>
<td>Serum cortisol (random)</td>
<td>&lt;15</td>
</tr>
<tr>
<td></td>
<td>15–33</td>
</tr>
<tr>
<td></td>
<td>&gt;33</td>
</tr>
<tr>
<td>ACTH stimulation test (delta)</td>
<td>&lt;9</td>
</tr>
<tr>
<td><strong>Relative Hypoadrenalism of Sepsis and Critical Illness</strong></td>
<td></td>
</tr>
<tr>
<td>Serum cortisol (random)</td>
<td>&lt;25</td>
</tr>
<tr>
<td>ACTH stimulation test (delta)</td>
<td>&lt;9</td>
</tr>
</tbody>
</table>
Corticosteroid Replacement

- Physiological Stress Dose
  - 200-300 mg qDay

- Replacement Strategy
  - Hydrocortisone 50-100 mg IV q6-8hr (“Stress Dose”)
    - Dexamethasone sub-optimal (no mineralocorticoid effect)
    - Mineralocorticoid (Fludrocortisone) not acutely required

- Measures will improve the blood pressure and clinical picture over 4-6 hour
Other Management

- Correct electrolytes/acidosis
  - rapid correction is generally seen with IV fluid and hydrocortisone administration
- Fluid resuscitation (NS 2-3L)
  - If more needed, consider changing to RL given concurrent risk of hyperchloremic metabolic acidosis in disease state + high volume saline input
- Dextrose for hypoglycemia
- Address precipitating factor/illness
**Treatment of Hypoadrenalism**

**Maintenance**
- Hydrocortisone 20 mg AM, 10 mg PM
- Fludrocortisone 100 μg/day

**Maintenance during Minor Illness**
- Hydrocortisone 40 mg AM, 20 mg PM
- Fludrocortisone 100 μg daily

**Coverage during Procedural Stress**
- Hydrocortisone 100 mg IV (one time only)

**Adrenal Crisis or Relative Adrenal Insufficiency of Critical Illness**
- Hydrocortisone 50–100 mg IV every 6 hr (OR)
- Hydrocortisone 50–100 mg IV followed by an infusion, 20 mg/hr
  - 0.9 NS 2–3 L over the first few hours
- Switch to Δ₉ NS if hypoglycemia
- Treat precipitating illness

Δ₉ NS, 5% dextrose in normal saline.
KEY CONCEPTS

- Thyroid storm is a life-threatening decompensation of severe hyperthyroidism precipitated by an intercurrent illness, typically sepsis. The hallmarks of thyroid storm include hyperthermia, exaggerated tachycardia, altered mental status, and gastrointestinal symptoms. Therapy of thyroid storm includes actions to reduce production of thyroid hormone, to inhibit thyroid hormone release, to block peripheral conversion of T₄ to T₃, to initiate beta-adrenergic blockade, to institute general supportive measures, and to identify and treat the precipitating event.

- Myxedema coma is a life-threatening deterioration of severe chronic hypothyroidism precipitated by an acute intercurrent illness. The prototypical case is an elderly woman in the winter who presents with marked hypothermia, altered mental status, respiratory failure, and hypotension. The management of myxedema coma requires immediate attention to airway management, fluid resuscitation, thyroid hormone replacement, general supportive measures, and treatment of the precipitating illness.

- Hallmarks of chronic adrenal insufficiency include generalized weakness, malaise, fatigue, gastrointestinal symptoms, weight loss, blood pressure less than 110/70 mm Hg, and hyponatremia. Primary autoimmune adrenal failure is the more common cause and is distinguished by the presence of hyperpigmentation, hyperkalemia, and more severe orthostasis. Hypopituitarism resulting in secondary adrenal insufficiency is distinguished by more severe hypoglycemia and the lack of the classic features seen in primary disease.

- Hypotension refractory to fluid resuscitation may be the only clue to the diagnosis of adrenal crisis or relative adrenal insufficiency of critical illness. In this setting, a random serum cortisol level should be obtained and IV hydrocortisone administered before confirmation is obtained.
References

- Zull D. Thyroid and Adrenal Disorders. *In: Rosen’s Emergency Medicine, Concepts and Clinical Practice. 7th ed.*
Corticosteriod Stress Dosing: Who? When? How much?

- **Who needs stress steroids?**
  - ?Addison’s
  - ?Chronic prednisone
  - ?Chronic Inhaled Steroids

- **When?**
  - ? Laceration suturing
  - ? Colle’s fracture reduction
  - ? Cardioversion for Afib
  - ? Trauma or septic shock

- **How Much?**
Effects of Exogenous Corticosteroids

- Hypothalamic – Pituitary – Adrenal axis suppression
  - Has occurred with ANY route of administration (including oral, dermal, inhaled, intranasal)
  - Adrenal suppression may last for up to a year after a course of steroids
  - HPA axis recovers quickly after prednisone 50 po od X 5/7
Streck 1979: Pituitary – Adrenal Recovery Following a Five Day Prednisone Treatment
Who needs Corticosteroid Stress Dosing?

- Coursin JAMA 2002: Corticosteroid Supplementation for Adrenal Insufficiency
  - All patients with known adrenal insufficiency
  - All patients on chronic steroids equivalent to or greater than PREDNISONE 5 mg/day
Corticosteroid Stress Dosing:
La Rochelle Am J Med 1993

- ACTH stimulation test to patients on chronic prednisone

- Prednisone < 5 mg/day
  - No patient had suppressed HPA axis
  - Three had intermediate responses

- Prednisone ≥ 5 mg/day
  - 50% had suppressed HPA axis, 25% were intermediate, 25% had normal response
Corticosteroid Stress Dosing

- What duration of prednisone is important?
- What about intermittent steroids?
- What about inhaled steroids?
Corticosteroid Stress Dosing:
Summary of literature review

- Short courses of steroids are safe
  - Many studies in literature documenting safety of prednisone X 5 – 10 days
- Wilmsmeyer 1990
  - Documented safety of 14 day course of prednisone
- Sorkess 1999
  - Documented HPA axis suppression in majority of patients receiving prednisone 10 mg/day X 4 weeks
- Many studies documenting HPA axis suppression with steroid use for > one month
Corticosteroid Stress Dosing

  - Adrenal suppression has occurred in moderate doses of ICS (Flovent 200 – 800 ug/day)
  - Adrenal suppression is more common and should be considered with chronic high doses of ICS (Flovent > 800 ug/day)
Corticosteroid Stress Dosing

- “There is NO consistent evidence to reliably predict what dose and duration of corticosteroid treatment will lead to H-P-A axis suppression.”

- Why?
Corticosteroid Stress Dosing: The bottom line

- Consider potential for adrenal suppression:
  - Chronic Prednisone 5 mg/day or equivalent
  - Prednisone 20 mg/day for one month within the last year
  - > 3 courses of Prednisone 50 mg/day for 5 days within the last year
  - Chronic high dose inhaled corticosteroids
When are stress steroids required?

- When is stress dosing required? (Cousin JAMA 2002)
  - Any local procedure with duration < 1hr that doesn’t involve general anesthesia or sedatives does NOT require stress dosing
  - All illnesses and more significant procedures require stress dosing
Corticosteroid Stress Dosing

MINOR Stress
Viral infection, URTI, UTI, fracture, etc, which do not require hospital admission

MODERATE Stress
Medical or traumatic conditions that require hospital admission

MAJOR Stress
Critical condition requiring ICU/CCU Emergent Surgery
Corticosteroid Stress Dosing

- **MINOR**
  - Double chronic steroid dose for duration of illness (only needs iv if can’t tolerate po)

- **MODERATE**
  - Hydrocortisone 50 mg po/iv q8hr

- **MAJOR**
  - Hydrocortisone 100 mg iv q8hr
Corticosteroid Stress Dosing

What about procedural sedation?

- Stress dose just before sedation/procedure
- Recommended by Coursin JAMA 2002 but NO supporting literature specific to procedural sedation in emerg
- Should be done ------> Hydrocortisone 50 mg iv just before procedure and then continue with normal steroid dose
Non-diabetic Endocrine Emergencies

- Recognize key features
- Pattern of underlying dz + precipitant
- Emergent management
  - P3S2, levothyroxine, dex
  - Supportive care and look for precipitant
- Consider corticosteroid stress dosing