Project: Ghana Emergency Medicine Collaborative

Document Title: Non-Diabetic Endocrine Emergencies

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NON-DIABETIC ENDOCRINE EMERGENCIES

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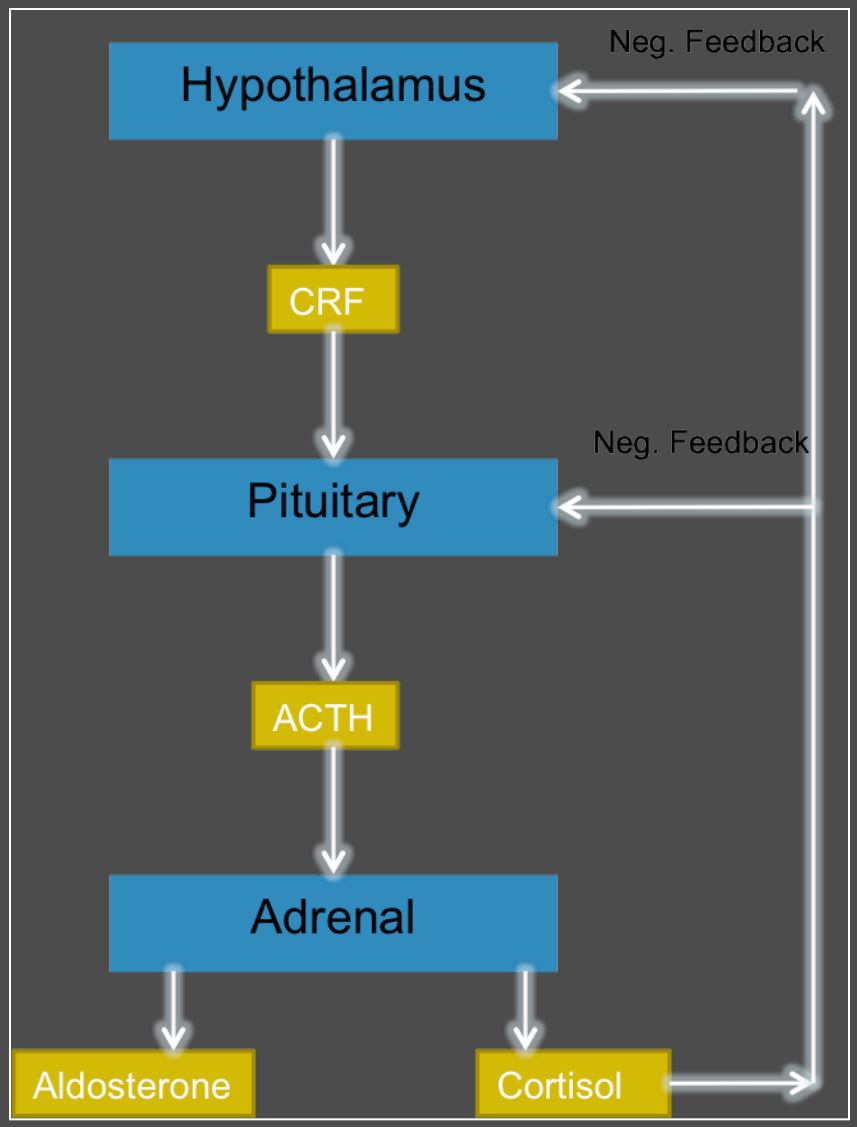

WHY?

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

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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?

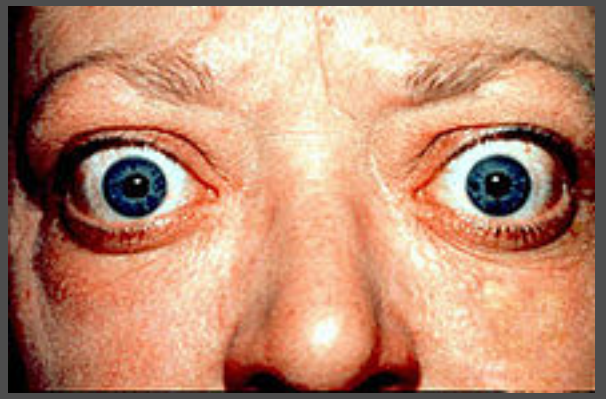
Background

- 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 39.8C
- Rapid Speech/Perseveration
- Tremulous



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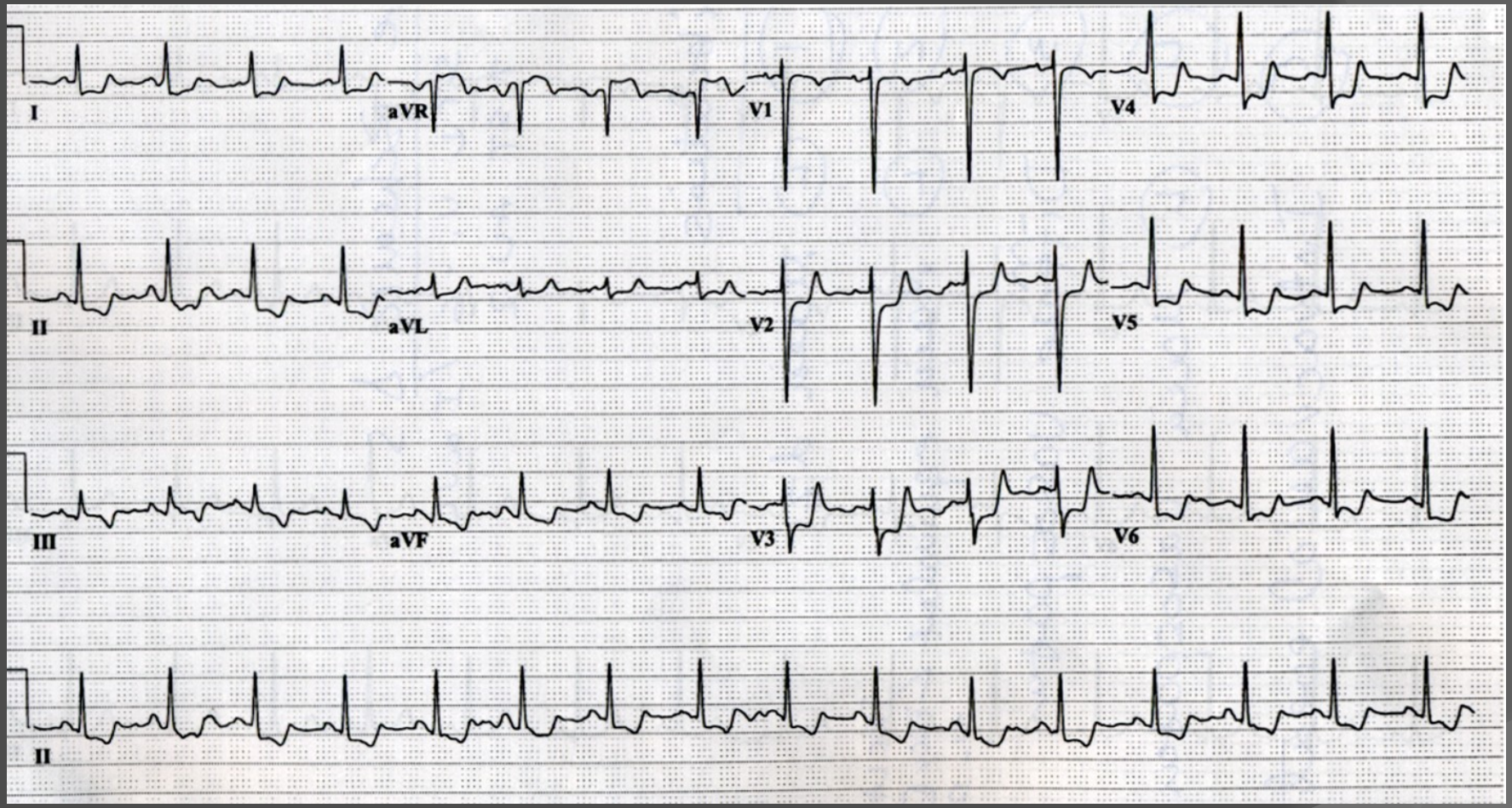

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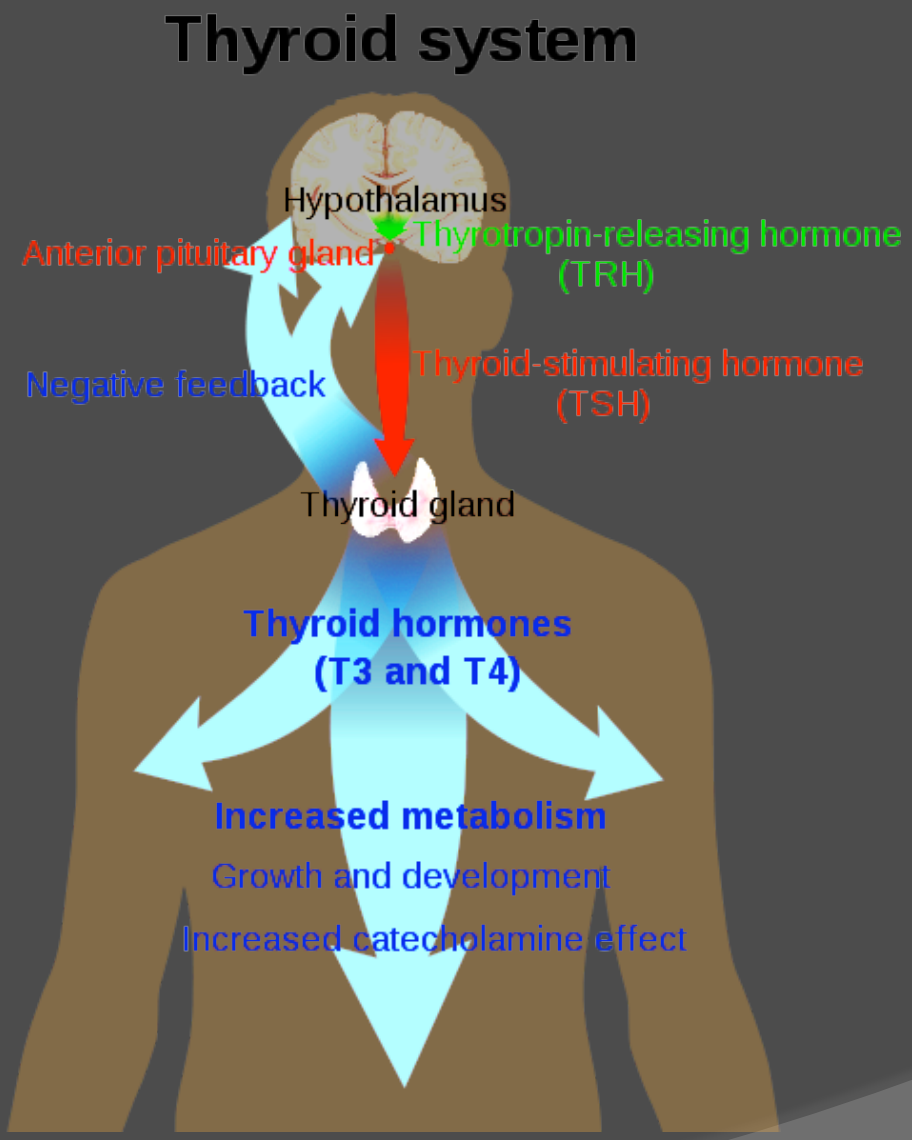
Definitions

- 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.

How Common?

- 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

Basic Science



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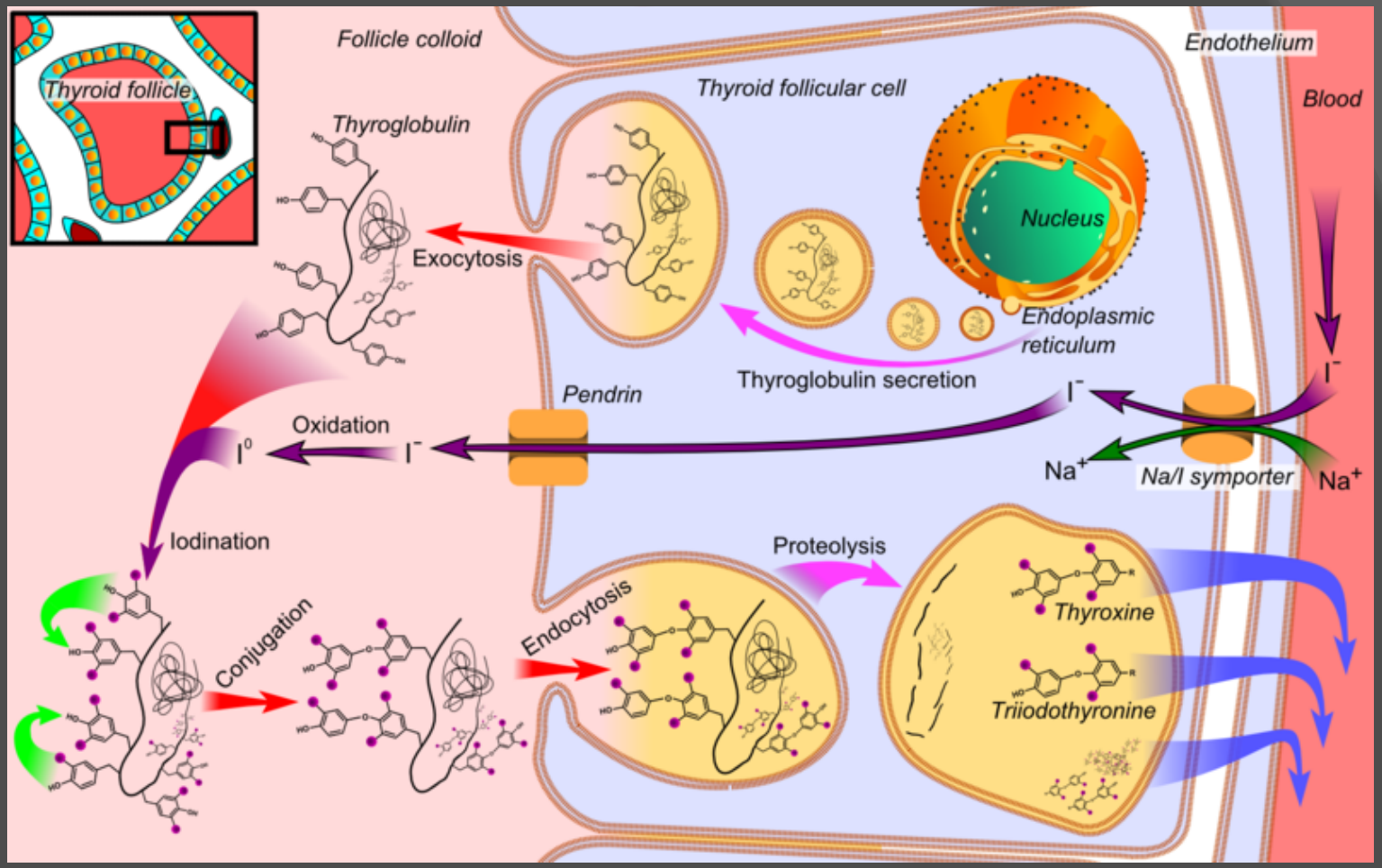
Biosynthesis

- 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 → 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.



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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

	Score
Fever (°F)	
99-99.9	5
100-100.9	10
101-101.9	15
102-102.9	20
103-103.9	25
≥104	30
Tachycardia (beats/min)	
90-109	5
110-119	10
120-129	15
130-139	20
≥140	25
Mental Status	
Normal	0
Mild agitation Delirium, psychosis	10
Extreme lethargy	20
Coma/seizures	30
Congestive Heart Failure	
Absent	0
Mild (edema)	5
Moderate (rales)	10
Pulmonary edema	15
Atrial fibrillation	10
Gastrointestinal and Hepatic Symptoms	
None	0
Nausea, vomiting Diarrhea, abdominal pain	10
Unexplained jaundice	20
Precipitating event	
None	0
Present	10
Tally the minimum score from each category. A score ≥45 suggests thyroid storm; a score of 25-44 suggests impending storm; and a score below 25 is unlikely to represent thyroid storm.	

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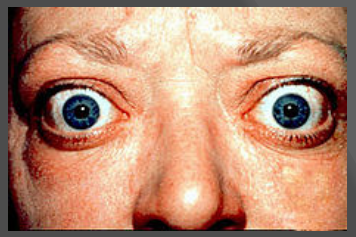
Thyroid Storm Diagnosis Criteria

- *Exaggeration of the clinical manifestions 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



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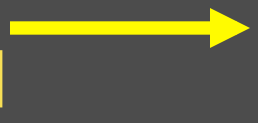
- **Constitutional:** Weight loss despite hyperphagia, fatigue, generalized weakness
- **Hypermetabolic:** Heat intolerance, cold preference, excessive perspiration
- **Cardiorespiratory:** Heart pounding and racing, dyspnea on exertion, chest pains
- **Psychiatric:** Anxiety, restlessness, hyperkinesis, 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

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

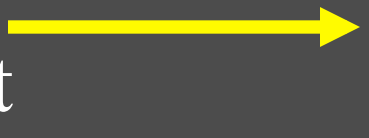
-Eyelids are sympathetically innervated so ↑ sensitivity to adrenergic stimuli in thyrotoxicosis leads to widening of the palpebral fissures

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

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

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

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

Patient Population Differences

- **The Elderly: Difficult to Diagnose
  - Fewer overt signs of hyperthyroidism
    - Cell surface β 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 β 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 T_4
- 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 T_4 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-lateralmembrane 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 Inhibitition 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
- STERIODS
- SUPPORTIVE CARE

P3S2

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, proponolol 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 Corticoesteroids (inhibit T_4 to T_3 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, intravaneous; NG, nasogastric; PO, by mouth; PR, in rectum; T_3, triiodothyronine; T_4, 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 → most convert via β blocker
  - Digoxin: increased clearance = higher dosing needed
    - Short Term: risk of SMA spasm → mesenteric ischemia
    - Long Term: digoxin toxicity associated with higher doses
  - Calcium Channel Blockers: Do not decrease heart work
  - Antocoagulation: 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
- Sildenifil

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, oriodides

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 (↑TSH, ↓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
  - Li_2CO_3 = 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 hypothyroid 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, cholestyramind, 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: phenytion, 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 arryhthmias
Myxdema facies: Puffy eyelids and lips, large tongue, broad nose
Evidence of severe chronic hypothyroidism: Skin, hair, reflexes, bradykinesis, voice
Acute precipitating illness (e.g., pneumonia)
Drug toxicity (e.g., sedative, narcotic, neuroleptic)
Hyponatremia

BOX 126-8 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.

PD-INEL 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
- Hypglycemia
  - 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.

BOX 126-11 TREATMENT OF MYXEDEMA COMA

Protect the airway/ventilatory support; monitor for alkalosis
Fluid resuscitation:
  0.9NS or D_5/0.9NS if hypoglycemia
  Watch for unmasking of CHF
Thyroid hormone replacement:
  T_4 alone (elderly and patients with cardiac comorbidity):
    T_4 300–500 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
  T_3 alone (younger patient, no cardiac risks; rapid correction desired):
    T_3 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 T_4 and T_3 therapy (intermediate approach):
    T_4 200–250 µg IV as initial bolus
    T_3 10 µg IV initial dose, then 10 µg IV every 8–12 hr
    T_4 100 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 D_5/0.9NS
  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; D_5/0.9NS, 5% dextrose in 0.9% normal saline; IV, intravenous; T_3, triiodothyronine; T_4, thyroxine.

PD-INEL Source Undetermined

Outcomes

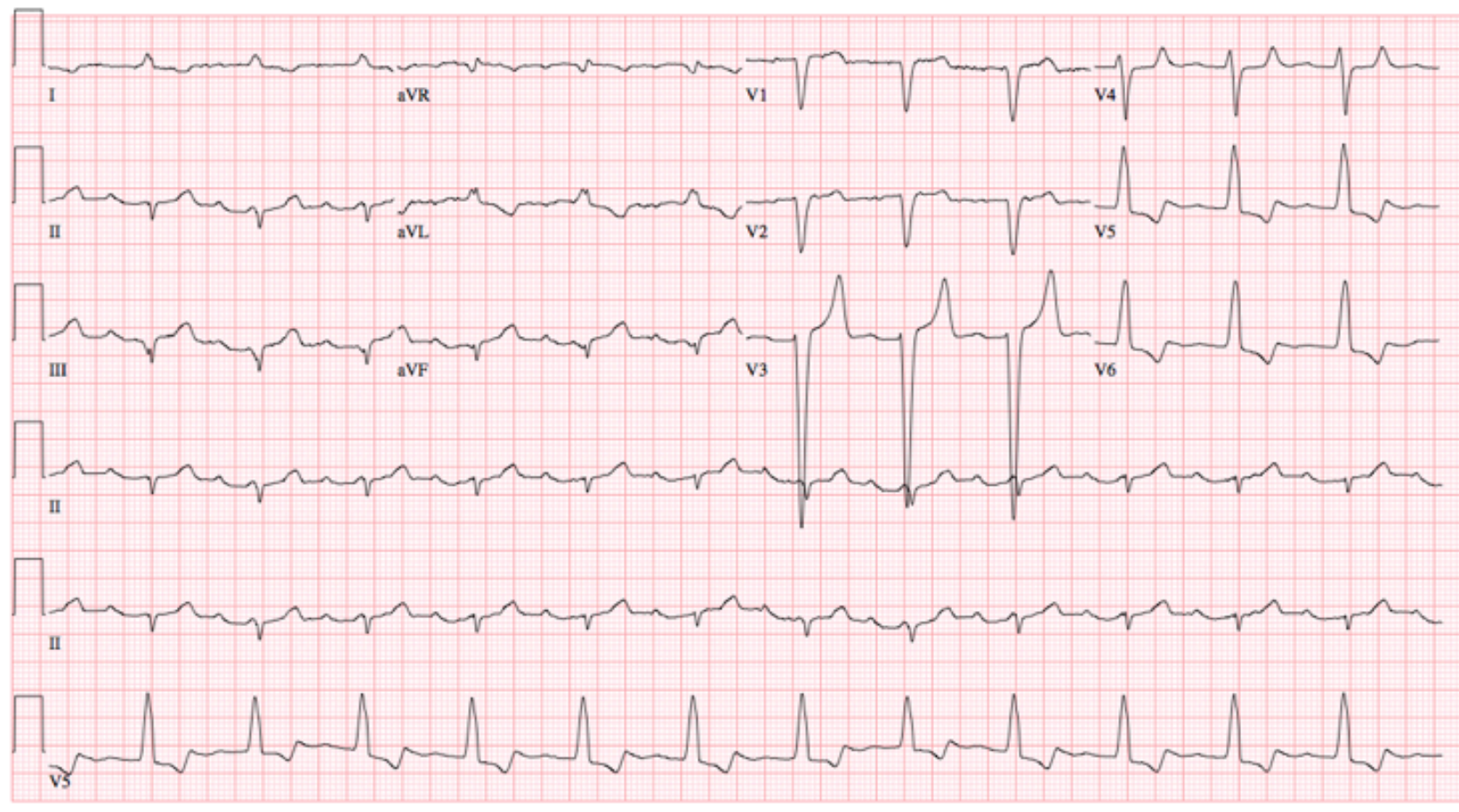
- Without thyroid hormone replacement and a vigorous approach, the mortality rate from myxedema coma exceeds 80%
- With rapid treatment and ICU care, rate falls to ≤ 20%.
- Factors that predict a poor outcome
  - advanced age, body temperature < 32C, hypothermia refractory to treatment, hypotension,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



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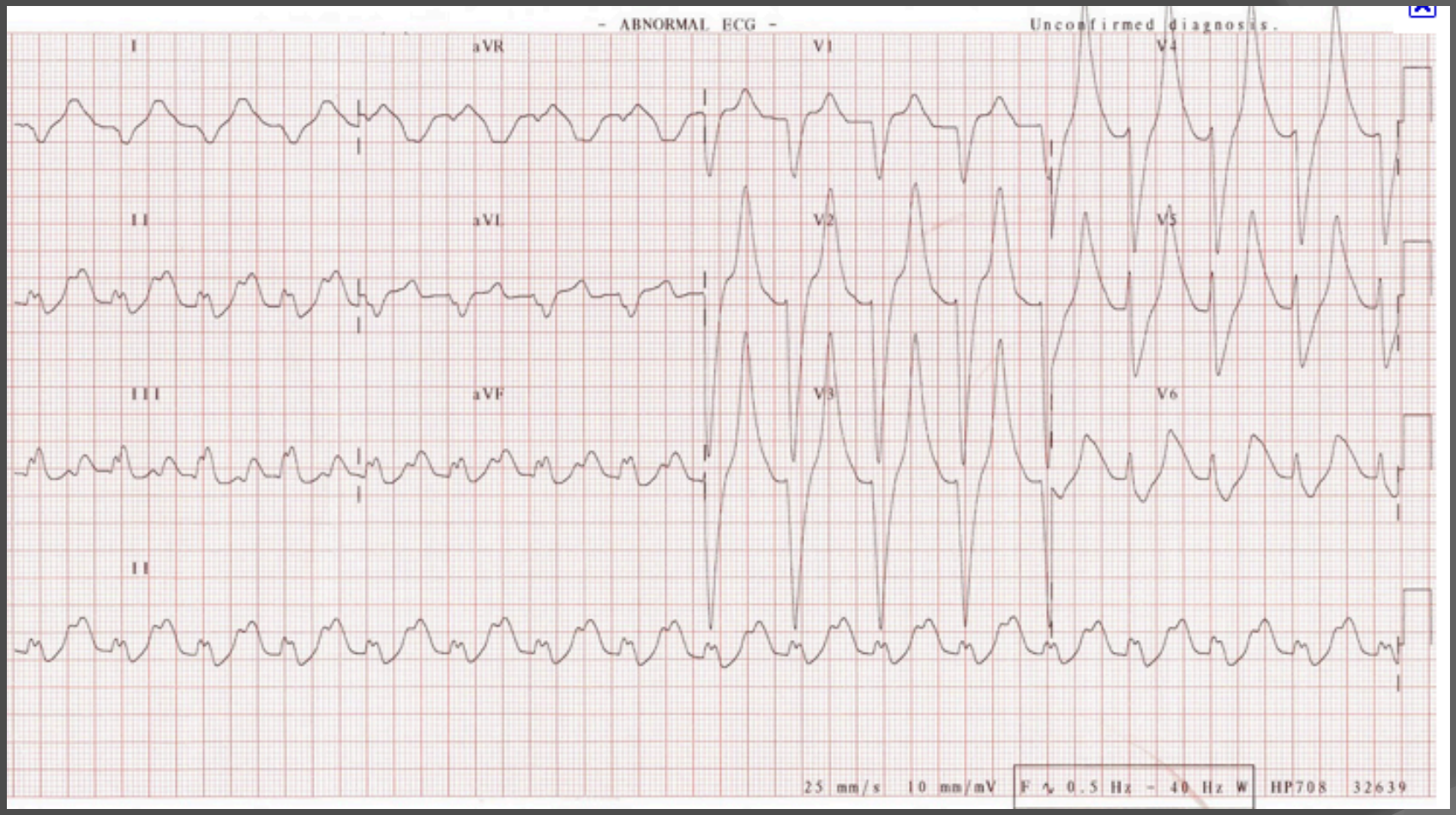
Source Undetermined

1300 hours at the Previous Hospital



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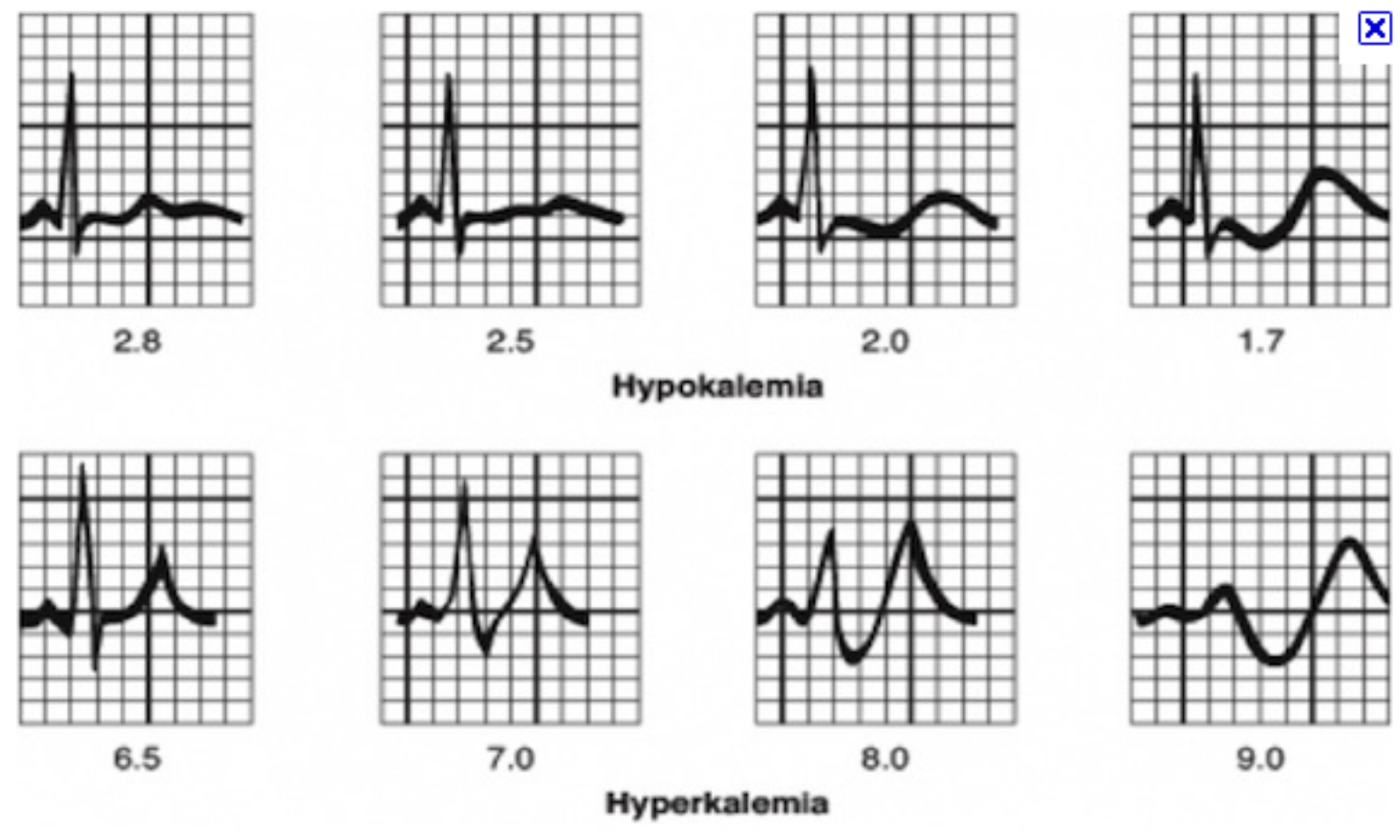
Source Undetermined

1345 hours (On Arrival ➔ Time to Treat)



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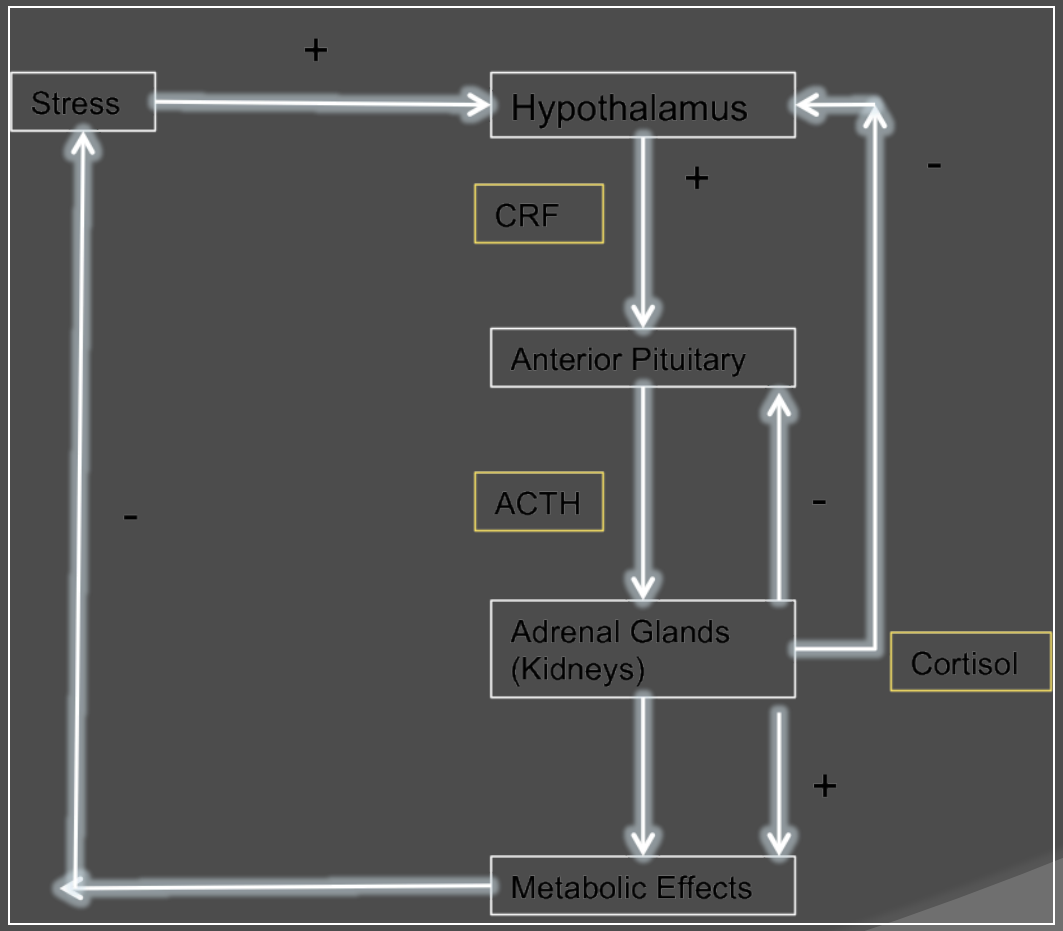
Source Undetermined

Adrenal Insufficiency



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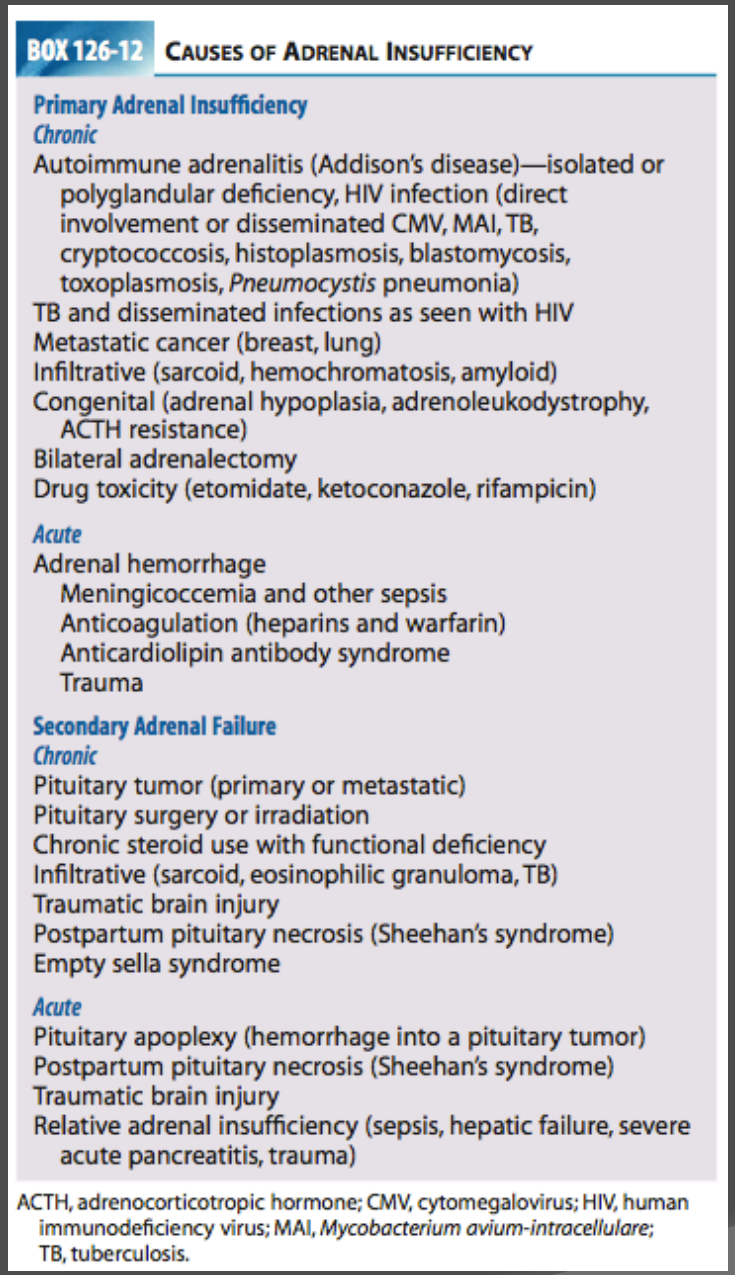
Lena Carleton, University of Michigan

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, adrenoleukodystrophy, ACTH resistance)
Bilateral adrenalectomy
Drug toxicity (etomidate, ketoconazole, rifampicin)

Acute

Adrenal hemorrhage
Meningicoccemia 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.

PD-INEL

Source Undetermined

Progression of Adrenal Crisis

Underlying Adrenal Insufficiency (Addision's and Chronic Steriods) → Acute Precipitant → Adrenal Crisis

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

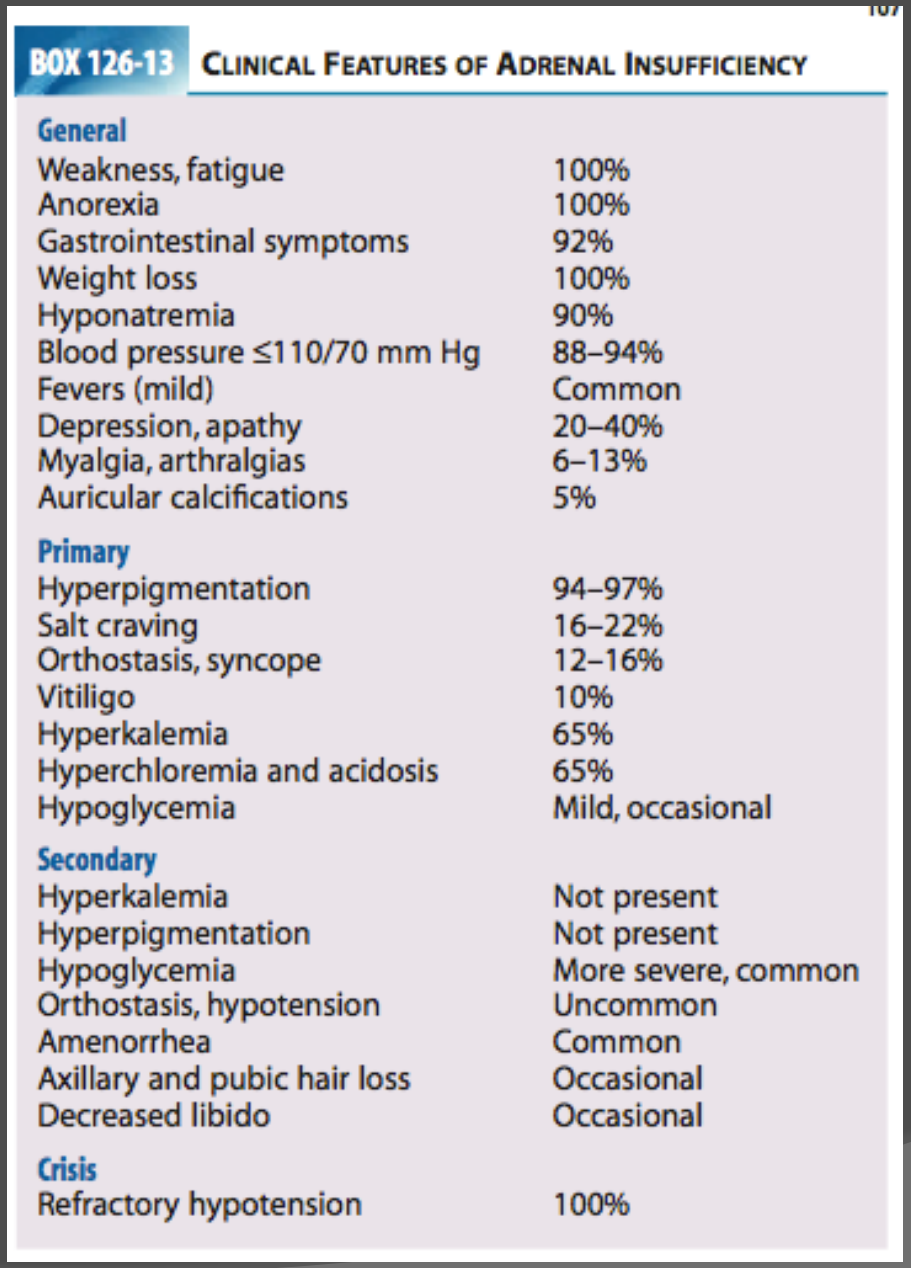
No known underlying Adrenal Insufficiency = Infarct/Hemorrhage?

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
  - ↓Na^+, ↑K^+
  - metabolic acidosis (↑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*



BOX 126-13 CLINICAL FEATURES OF ADRENAL INSUFFICIENCY

General	
Weakness, fatigue	100%
Anorexia	100%
Gastrointestinal symptoms	92%
Weight loss	100%
Hyponatremia	90%
Blood pressure ≤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%

PD-INEL Source Undetermined

Hyperpigmentation

PD-SELF FlatOut, Wikimedia Commons

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Hyperpigmentation

- ACTH
  - Share POMC precursor with melanocyte-stimulating hormone (MSH)
    - POMC cleavage → ACTH, γ-MSH, β-lipoprotein
    - ACTH subunit further cleavage → α-MSH *(pigments skin)*
    - Given ↓ feedback on Ant Pituitary → ↑ACTH

Investigations

- Adrenal Function
  - ✓Electrolytes
    - *Random cortisol*
    - *ACTH*
- Look for Precipitant
  - ECG
  - CXR
  - Labs
  - Urinalysis
  - ±EtOH/Tox panel

Electrolyte Derangement

- Adrenal gland failure → ↓aldosterone, ↓Na^+
- Cortisol deficiency → ↑ADH → ↑Free H_20
  - 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 126-3 Diagnosis of Hypoadrenal States

	LEVEL (μg/dL)	DIAGNOSTIC CONCLUSION
Chronic, Nonstressed		
Serum cortisol (6–8 AM)	<3	Diagnostic
	<10	Suggestive
	10–20	Normal
	>20	Excludes
ACTH stimulation test (peak)	<20	Diagnostic
	>20	Excludes
Acute Crisis		
Serum cortisol (random)	<15	Diagnostic
	15–33	Indeterminant
	>33	Excludes
ACTH stimulation test (delta)	<9	Diagnostic
Relative Hypoadrenalism of Sepsis and Critical Illness		
Serum cortisol (random)	<25	Likely
ACTH stimulation test (delta)	<9	Diagnostic

PD-INEL

Source Undetermined

Corticosteroid Replacement

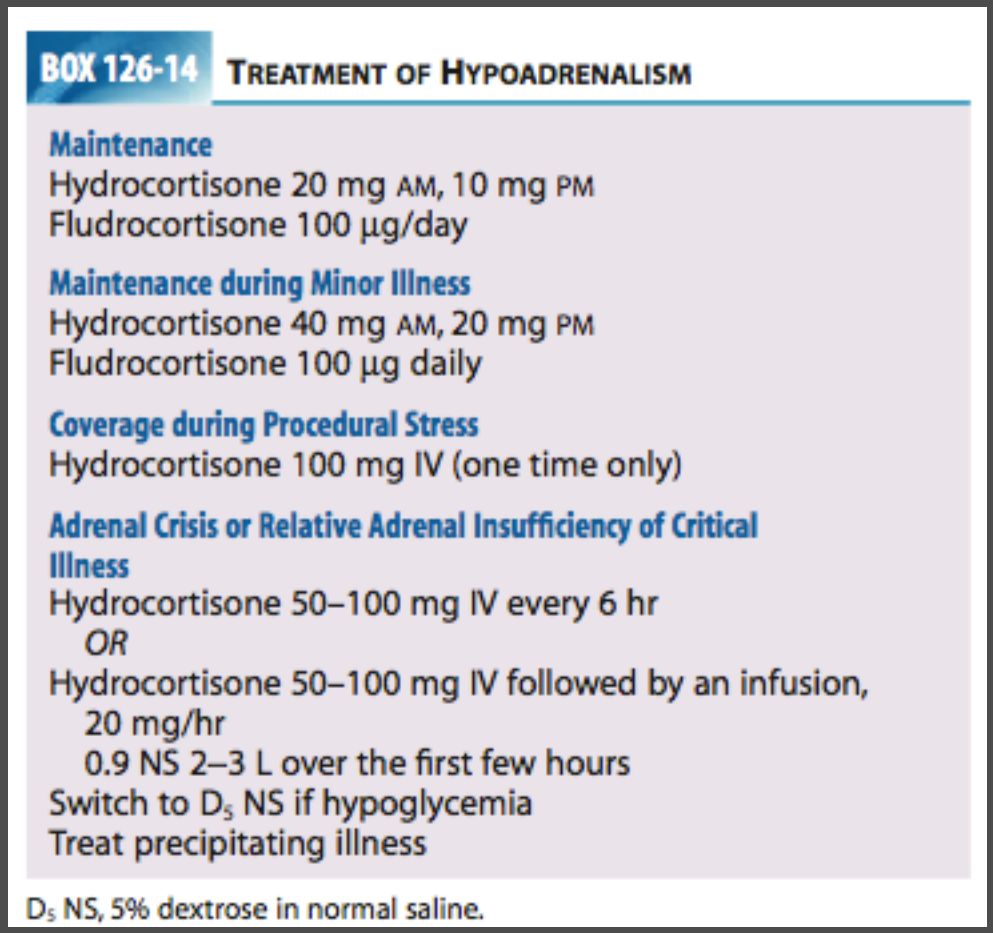
- Physiologial Stress Dose
  - 200-300 mg qDay

- 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



BOX 126-14 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 D_5 NS if hypoglycemia
Treat precipitating illness

D_5 NS, 5% dextrose in normal saline.

PD-INEL

Source Undetermined

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 T_4 to T_3, 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.

PD-INEL

Source Undetermined

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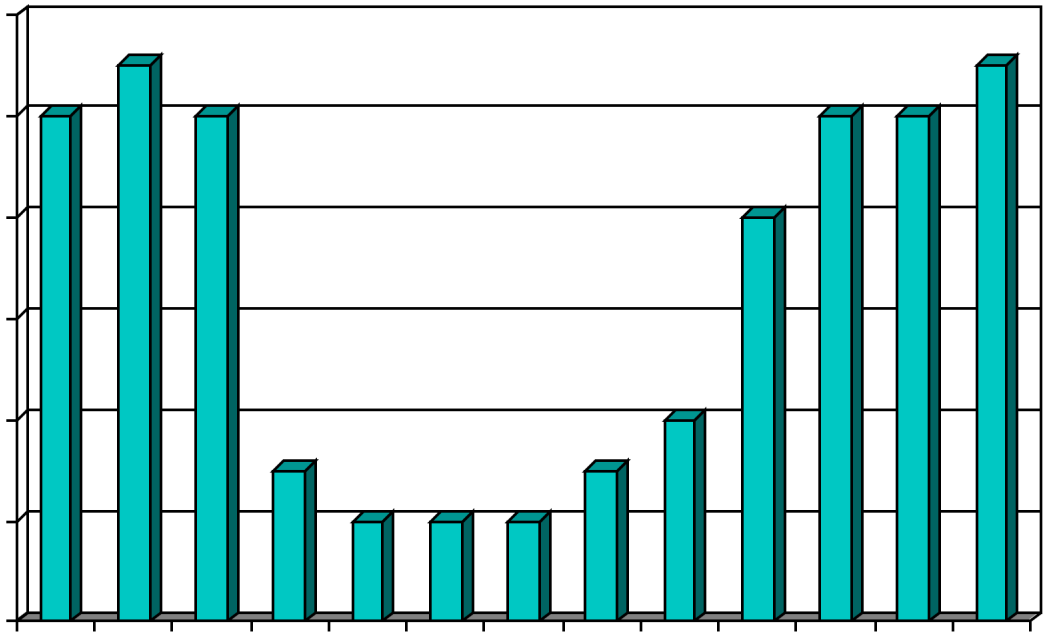
Corticosteriod Stress Dosing: Who? When? How much?

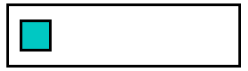
- Who needs stress steroids?
  - ?Addison's
  - ?Chronic prednisone
  - ?Chronic Inhaled Steroids
- When?
  - ? Laceration suturing
  - ? Colle's fracture reduction
  - ? Cardioversion for Afib
  - ? Trauma or septic shock
- How Much?

Effects of Exogenous Corticosteroids

- Hypothalamic – Pituitary – Adrenal axis suppression
  - Has occurred with ANY route of administration (including oral, dermal, inhaled, intranasal)
  - Adrenal suppresion 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





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Source Undetermined

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 > or = 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

- Inhaled Corticosteroids: Allen 2002. Safety of Inhaled Corticosteroids.
  - 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?*

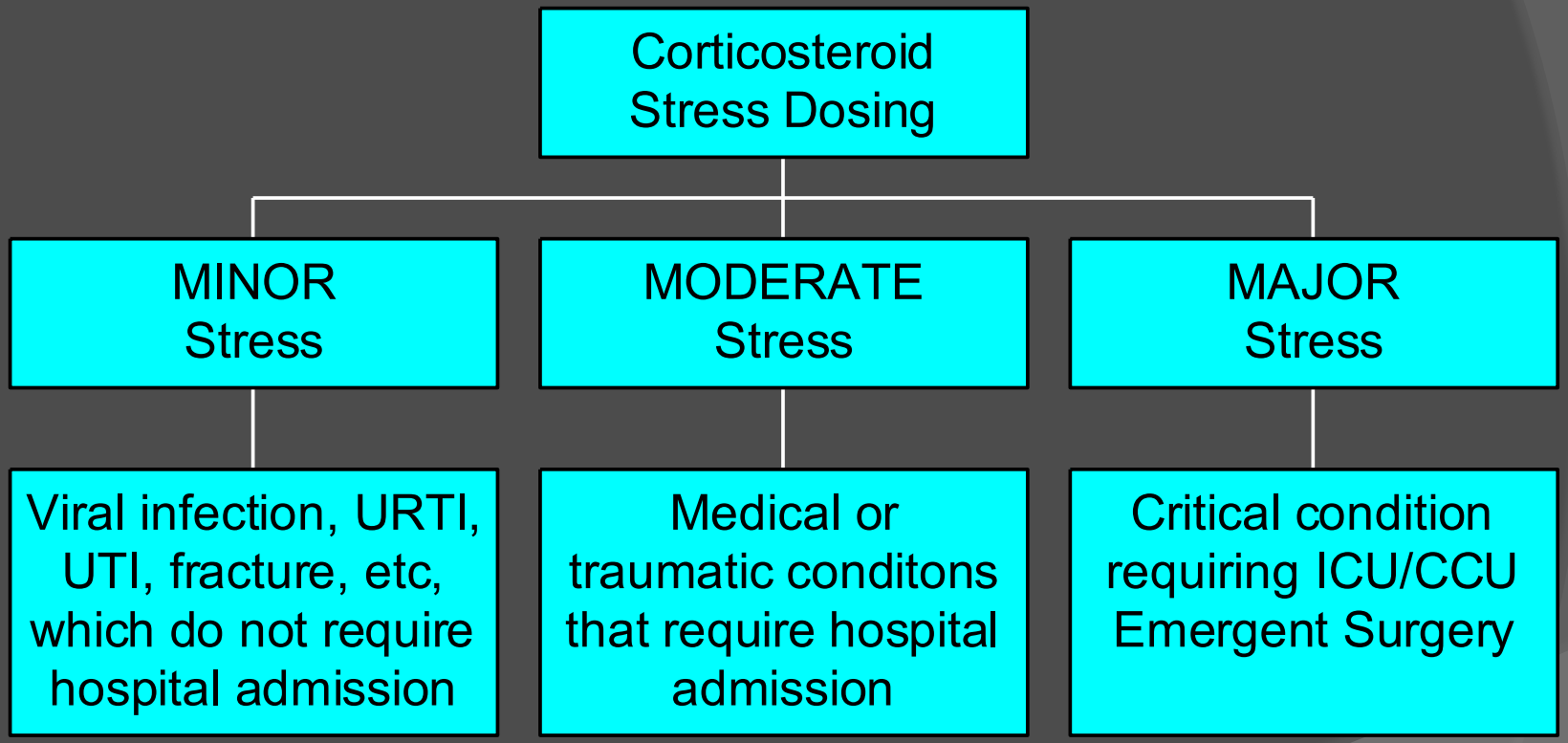
Corticosteroid Stress Dosing:
The bottom line

- 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



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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