Endocrine Emergencies

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Case #1

- 21-year old WF presents with dyspnea and abdominal pain. She has been complaining of thirst, polyuria, and blurred vision for a week while studying for final exams. She had a cold two weeks ago.
- HR 100, BP 100/60 supine, 90/50 upright
- Ph Ex: flat neck veins, fruity breath, diffuse abdominal tenderness

Case #1

- Glucose 320 mg/dl
- Bicarbonate 5 mEq/l
- Urine ketones 3+
- Sodium 129 mg/dl
- Potassium 5.5 mmol/l
- WBC 12,000/ m^3
- ECG: Sinus tachycardia
- What is the diagnosis?

Diabetic Ketoacidosis

Pathogenesis of Diabetic Ketoacidosis (DKA)

Main Components:

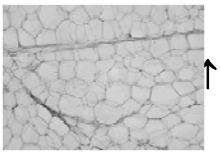
- ✓ HYPERGLYCEMIA
- ✓ KETOSIS
- ✓ ACIDOSIS

ADIPOSE
↓Glucose Uptake
↑Lipolysis

MUSCLE
↓Glucose Uptake
↑Proteolysis

LIVER
↑ Glycogenolysis
↑ Gluconeogenesis

Ketogenesis



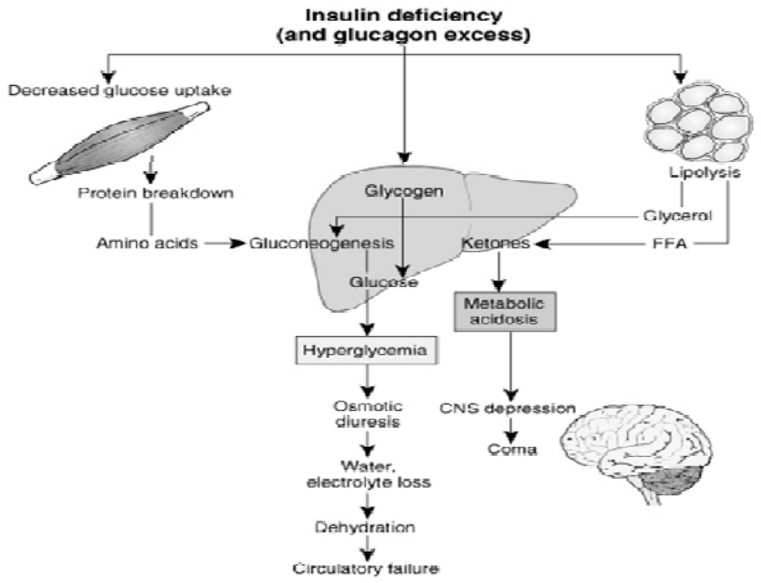
Adipose image - Courtesy of Department of Histology, Jagiellonian University Medical College

Diabetic Ketoacidosis (DKA)

- Deficiency of insulin →
  - Increased hepatic glucose production → Hyperglycemia
  - Increased lipolysis → gluconeogenic precursors (glycerol) to liver → gluconeogenesis → Hyperglycemia
  - Increased proteolysis → gluconeogenic precursors (amino acids) to the liver → gluconeogenesis → Hyperglycemia
  - Impaired glucose uptake in muscle and fat → Hyperglycemia
  - Increased lipolysis → FFA → ketone production and ketoacidosis
- Glucagon excess → Increased glycogenolysis, gluconeogenesis, and ketoacid production

Porth's Pathophysiology: Concepts of Altered Health States, 7th ed. Lippincott Williams & Wilkins, 2005

Diabetic Ketoacidosis (DKA)



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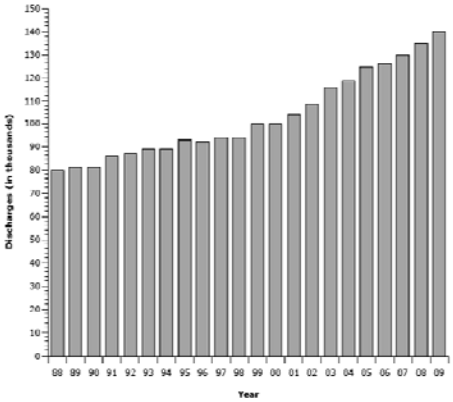
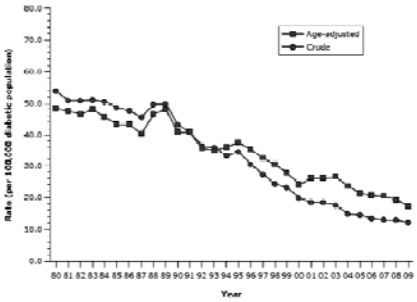
Diabetic Ketoacidosis (DKA)



Number (in thousands) of hospital discharges with diabetic ketoacidosis as first-listed diagnosis, United States, 1988 to 2009



Crude and age-adjusted death rates for hyperglycemic crises as underlying cause per 100,000 diabetic population, United States, 1980 to 2009

Images from Centers for Disease Control and Prevention - www.cdc.gov

Symptoms and Signs of DKA

- Polyuria
- Polydipsia
- Nausea and vomiting
- Abdominal pain
- Weakness
- Depressed sensorium
- Blurry vision
- Hyperventilation with Kussmaul respirations
- Fruity breath (Acetone)
- Shock
- Signs of dehydration
- Signs and symptoms related to precipitants

DKA Physical Examination

- Vital Signs: Tachycardia, tachypnea (metabolic acidosis), hypotension, orthostasis
- Mental Status: Lethargy, coma
- Dehydration: flat neck veins, dry mucous membranes
- Respiratory: Deep, rapid respirations (Kussmaul), fruity breath odor (acetone)
- Abdomen: Tenderness, guarding (may mimic acute abdomen)

Precipitating factors for DKA

- New-onset diabetes (20-25%)
- Noncompliance with insulin therapy
- Infection (30-40%) (pneumonia and UTI most common)
- Myocardial infarction
- Alcohol and/or drug abuse (Cocaine)
- Stroke
- Acute Pancreatitis
- Surgery
- Endocrinopathies
  - Acromegaly
  - Thyrotoxicosis
  - Cushing's Syndrome
- Trauma
- Drugs
  - Corticosteroids
  - High dose thiazide diuretics
  - Antipsychotics
- Hot weather and insufficient water

Laboratory Features Diagnostic for DKA

- Serum glucose > 250 mg/dL (13.9 mmol/L)
- Arterial pH < 7.35 (venous pH <7.3)
- Serum bicarbonate < 18 mEq/L
- Serum acetone test positive
- Urinary ketone test positive (3+)

Additional Laboratory Features Consistent with DKA

- WBC count elevated (but < 25,000/mm^3)
- Anion gap > 12
- $PaCO_2$ < 40 mm
- Na^+ normal or low
  - Pseudohyponatremia
- Measured serum K^+ high, normal, or low
- Triglycerides normal or elevated

DKA Additional Evaluation

- CBC with Differential
- Urinalysis with Culture and Sensitivity
- Chest X-Ray ("rule out pneumonia")
- Electrocardiogram
- If applicable:
  - Blood culture
  - Toxicology screen

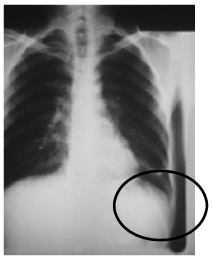


Image from CDC Public Health Image Library

Essential Management of DKA

- Appropriate intravenous fluid resuscitation
- Continuous insulin administration
- Potassium replacement

DKA Treatment

- IVF: 0.9% Normal saline at 15-20 mL/kg/lean body weight per hour (typically 1 liter/hour) for the first 4 hrs
  - Change IV fluid to Dextrose 5% 0.45% NaCl when glucose < 250 mg/dL
- IV drip: Regular human insulin (100 U/mL) at 0.1-0.15 U/kg/hr (typically 5-10 U/h)
  - Expect glucose to decrease by ≥ 75 mg/dL/hr

DKA Treatment (continued)

- If hypokalemic (<3.3), give K^+ before insulin bolus
  - Patient is whole body potassium depleted (300-600 mEq) due to gastrointestinal and renal (osmotic diuresis) losses
  - Hyperkalemia may occur due to insulin deficiency and acidosis (ICF to ECF)
  - Potassium will drop rapidly once insulin is given – promotes intracellular K^+ entry
  - Initiate replacement when measured serum K^+ < 5.4 mmol/L

DKA: Signs of Recovery and Transition off IV Insulin

- Venous pH $\geq$ 7.3
- Arterial pH $\geq$ 7.35
- Bicarbonate $\geq$ 18 mEq/L
- Anion gap $\leq$ 14
- Patient tolerating PO intake
- MUST give a dose of long-acting insulin SQ, 120 minutes before stopping IV insulin drip

Case #2

- 63-year-old WF presents with obtundation. Her daughter had not seen her in a week, but she had been complaining of thirst and blurred vision.
- PMH: "Sugar diabetes" for which she takes pills, HTN, arthritis
- P Ex: HR 100, BP 100/60 supine
- Overweight, flat neck veins

Case #2

- Glucose 600 mg/dl
- Bicarbonate 24 mEq/l
- Urine ketone: Trace positive
- Sodium 145 mmol/l
- Potassium 5.5 mmol/l
- BUN 40, Creatinine 1.8 mg/dl
- What is the diagnosis?

Hyperosmolar Hyperglycemia Syndrome

Hyperosmolar Hyperglycemia Syndrome (HHS)

- Typically complication of type 2 diabetes
- Older patients
- High mortality (up to 60%)
- Profound hyperglycemia (600-3000 mg/dL)
- Hyperosmolality (> 320 mOsm/kg)
- Severe dehydration
- Often present with impaired mental status or coma

Hyperosmolar Hyperglycemia Syndrome (HHS)

LIVER
↑Gluconeogenesis
↑Glycogenolysis

MUSCLE
↓Glucose Uptake

HYPERGLYCEMIA

HYPEROSMOLALITY

Author:
Mikael Häggström

PANCREAS
Glucose Toxicity

KIDNEYS
↓Glucose Excretion

Comparison of DKA and HHS

	DKA	HHS
*Glucose	250 to 800	600 to >1000
Osmolarity	Variable	>320
**Urinary ketones	++	Trace + or negative
**BHB	+	-
pH	< 7.3	>7.3
Bicarbonate	<18	>18
**Anion Gap	>15	<15
Precipitating illness	Yes	Yes
Mortality	+	++
Age	Young	Elderly

***Two factors contribute to less severe hyperglycemia in DKA:**
Earlier presentation of symptoms
Younger patients have a higher GFR and more glucosuria
**** Absence of ketogenesis in HHS due to relative as opposed to absolute insulin deficiency**

Management of HHS

- Intravenous fluid resuscitation
  - Isotonic fluid (0.9% NaCl) initially
  - Hypotonic fluid (0.45% NaCl) when BP stabilizes
  - Add Dextrose 5% when glucose $\leq$ 250 mg/dL
- Insulin administration
  - Similar to DKA
  - May wait until hemodynamically stable
  - Avoid over-correction of glucose

Case #3

- 45-year old WM with type 1 diabetes is admitted for R/O MI. Started on NPH BID and sliding scale Humalog QAC and HS.
- At 10:30 pm, patient calls nurse reporting that he feels "funny."
- At 11:00 pm, nurse finds patient diaphoretic and mumbling incoherently.
- What is the diagnosis?

Hypoglycemia

Clinical Manifestations of Hypoglycemia

Neurogenic

- Sweating
- Hunger
- Paresthesias
- Tremor
- Palpitations
- Anxiety
- Tachycardia
- Hypertension

Neuroglycopenic

- Warmth
- Weakness
- Confusion
- Drowsiness
- Dizziness
- Blurred Vision
- Focal Neurologic Sx.
- Hypothermia

Glucose Regulation

Hyperglycemia

↑ Insulin

Hypoglycemia

↓ Insulin
↑ Glucagon
↑ Epinephrine
↑ Cortisol
↑ Growth Hormone

Treatment of Hypoglycemia

- Do not overtreat !!
- PO route preferred
  - 10-20 gms and recheck in 15 minutes and repeat
- IV dextrose
  - 12.5 gms (1/2 amp D50)-full 25 gm
  - Double current dextrose infusion
- Glucagon (if no IV) in thigh or abdomen
  - 1 mg (IM, SQ, IV)
  - Response takes 10 to 15 minutes
  - Followed by PO or IV glucose +/- protein
  - Nausea occurs in 60 to 90 minutes

Case #4

- A 32-year old WF presents to the ED with severe abdominal cramping, nausea and vomiting.
- PMH: Type 1 diabetes mellitus, Hashimoto's thyroiditis
- HR 110, BP 100/60 supine, 90/50 upright
- P Ex: Flat neck veins, diffuse abdominal tenderness, hyperpigmentation

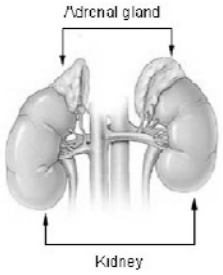
Case #4

- Glucose 95 mg/dl
- Bicarbonate 24 mEq/l
- Urine ketone: Negative
- Sodium: 128 mmol/l
- Potassium: 5.5 mmol/l
- ECG: Sinus tachycardia
- What is the diagnosis?

Adrenal Insufficiency

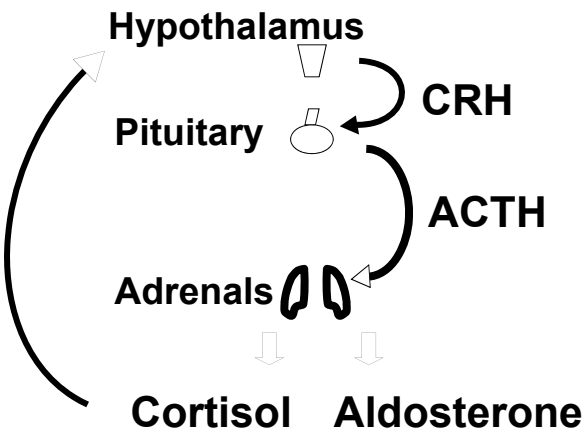
Normal adrenal function

- Adrenal Cortex
  - CORTISOL (glucocorticoid)
  - ALDOSTERONE (mineralocorticoid)
  - ANDROGENS (sex steroids)
- Adrenal Medulla
  - Catecholamines

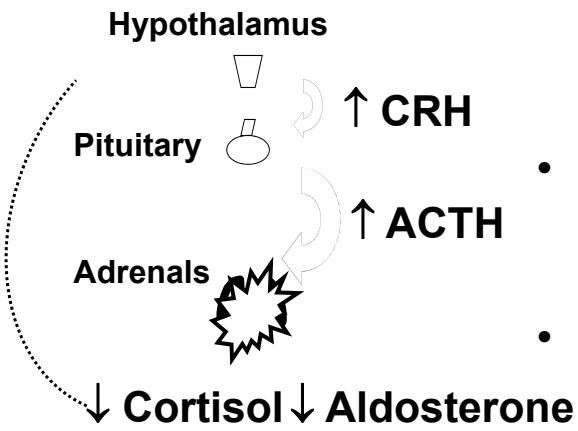


Author: EEOC - cancer.gov

Adrenal Feedback



Primary Adrenal Insufficiency



- **Primary**
  - Adrenal gland
  - Destruction of glands
- **Secondary**
  - Pituitary
  - Inadequate ACTH
- **Tertiary**
  - Hypothalamic
  - Iatrogenic
  - Inadequate CRH

Addison's Disease

Source: U.S. National Archives and Records Administration

Genetic/Syndromic Causes of Primary Adrenal Failure

Typically presenting early in life (<1 yr)

- **CAH (steroid biosynthesis defect)**
- **Adrenal Hypoplasia Congenita (defect in adrenogenesis or adrenal development in 1st trimester)**
  - **Low cortisol and aldosterone**

Typically presenting in childhood, and presentation is usually syndrome

- **Triple A syndrome**
  - **ACTH resistant cortisol deficiency, achalasia, absent lacrimation**
- **APS Type I (APECED or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy)**
  - **Hypopara, mucocutaneous candidiasis, primary AI**

Genetic/Syndromic Causes of Primary Adrenal Failure (continued)

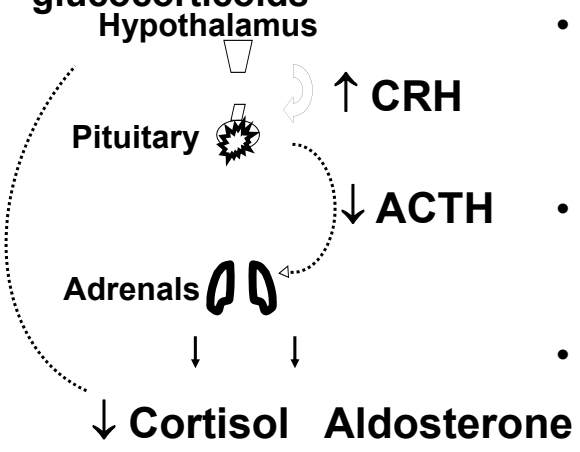
- Presenting in adulthood
  - APS Type II (Type I DM, thyroid disease), ?non-classical CAH

Non-inherited Types

- Adrenal hemorrhage
  - Waterhouse-Friederichson syndrome
    - Meningococcal sepsis
  - Other pathogens (P. aeruginosa, S. pneumoniae, Staph aureus, Group B strep)
- HIV
- Autoimmune
  - Either in setting of other findings of APS II, or not
- Adrenalectomy

Secondary Adrenal Insufficiency

In most cases, primary adrenal failure will involve *both* gluco- and mineralocorticoids, whereas secondary failure will be specific for glucocorticoids

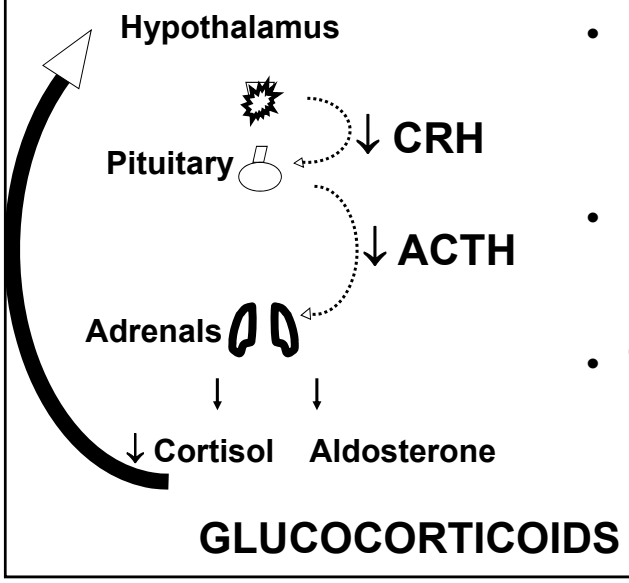


- Primary
  - Adrenal gland
  - Destruction of glands
- Secondary
  - Pituitary
  - Inadequate ACTH
- Tertiary
  - Hypothalamic
  - Iatrogenic
  - Inadequate CRH

Secondary Adrenal Failure

- Pituitary malfunction
  - Tumor destroying normal cells
  - Autoimmune hypophysitis
    - May be quite specific for loss of ACTH-producing cells
  - Infiltrative diseases of pituitary
    - Histiocytosis X
    - Sarcoidosis

Tertiary Adrenal Insufficiency



- **Primary**
  - Adrenal gland
  - Destruction of glands
- **Secondary**
  - Pituitary
  - Inadequate ACTH
- **Tertiary**
  - Hypothalamic
  - Iatrogenic
  - Inadequate CRH

Features of Chronic Adrenocortical Insufficiency

•Weakness, fatigue	100%
•Weight loss	100%
•Anorexia	100%
•Hyperpigmentation	92%
•Hypotension	88%
•Nausea, abdominal pain	56%
•Salt craving	19%

Treatment of Adrenal Insufficiency Glucocorticoids

- Glucocorticoids: Hydrocortisone (Short acting)
  - Metabolized from cortisone to cortisol
  - Approx 12-15 mg/m^2 is replacement dose of HC
  - In most people, this is about 20-25 mg/day
  - Mimic the diurnal variation (2/3 steroid A.M.; 1/3 evening)
    - Evening dose given mid afternoon (e.g., 3pm) unless patient is night owl
  - Other steroids (Long acting)
    - Prednisone ~5 mg/day
    - Dexamethasone ~0.5 mg/day (but rarely used for replacement)

Adrenal Crisis

- Acute loss of adrenal function
  - Acute loss of adrenals
    - Surgery
    - Hemorrhage/thrombosis
  - Acute loss of pituitary function
  - Acute loss of steroid replacement

OR

- Acute stress in the setting of compensated chronic adrenal failure
  - Precipitating event (e.g., like DKA)

Features of Acute Adrenocortical Insufficiency (Adrenal Crisis)

- Hypotension
- Weakness (proximal muscles), confusion
- Nausea, vomiting, abdominal pain
- Hyponatremia/Hyperkalemia
- Dehydration, hypovolemia
- Hyperthermia
- Hypoglycemia

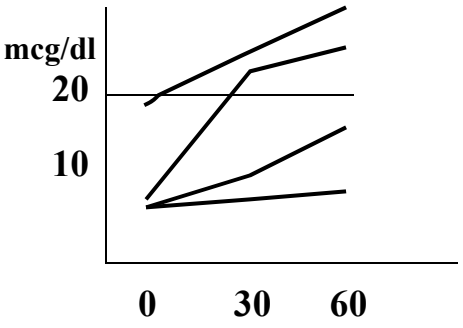
TREAT FIRST, AND DIAGNOSE LATER!!

Diagnosis of Adrenal Insufficiency

- ACTH stimulation test
  - 250 mcg IV x 1
  - Role of 1 mcg ACTH stim test??
- ACTH measurement (for differential dx)
- Random cortisol
  - Great test…when negative.
    - (e.g., a random cortisol of 30)
  - Decent test…when positive.
  - Often useless!

ACTH Stimulation Test

- Tests for <u>adrenal insufficiency</u>
  - Give IV bolus of 250 mcg ACTH
  - Measure cortisol at 0, 30, 60 minutes
- Normal response to >18 mcg/dl
  - Alternate endpoints in the literature:
    - Should be also 2-3x basal level
    - Increment of 9



Treatment of adrenal crisis

- Hydrocortisone: 200-300 mg/day (100 mg IV bolus)
  - Patients with known adrenal insufficiency
  - Severe stress (e.g., sepsis, surgery, burn – ICU)
  - Typically given on TID basis (100 mg TID)
- Dexamethasone: 8-16 mg/day (4 mg IV bolus)
  - "Neurosurgical" doses may be higher
  - Not measured in serum cortisol assays, so can still perform ACTH stim test in acute setting
  - Lacks mineralocorticoid activity, so patients may require pressors

Treatment of Adrenal Insufficiency: Mineralocorticoids

- Replacement of mineralocorticoid needed if primary adrenal failure (e.g., adrenalectomy) but not for secondary
  - Florinef is synthetic mineralocorticoid (fludrocortisone)
  - Comes in only 1 size (100 mcg)
  - Most patients need 1 tab/day, but may need to titrate to symptoms or electrolytes
  - In patients on high dose HC (>50 mg/day), enough MC activity so that supplementation is not needed

Thyroid Emergencies

Hyperthyroidism vs thyrotoxicosis

- Thyrotoxicosis is the syndrome of too much thyroid hormone
- Hyperthyroidism is overactivity of thyroid gland
  - Always associated with thyrotoxicosis

maybe

- For example, ingesting large amounts of thyroxine causes thyrotoxicosis but NOT hyperthyroidism

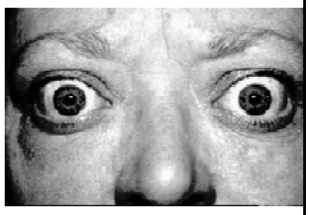
Symptoms of Hyperthyroidism

- Hyperactivity
- Nervousness
- Emotional lability
- Heat intolerance
- Sweating
- Tremors
- Palpitations
- Weight loss
- Hyperphagia
- Diarrhea
- Oligo/amenorrhea
- Trouble sleeping
- Weakness
- Others:
  - Changes in the neck
  - Diffuse enlargement (goiter)
  - Single lump (nodule)
  - Eye changes (Graves disease ONLY)
  - Neck pain (suggests thyroiditis)
  - Post-partum state
  - Family history (?)

Weight loss, CV problems, weakness, r/o depression may be signs of apathetic hyperthyroidism in the elderly

Physical Exam

- General:
  - Anxious, fidgety
- Vital signs:
  - Tachycardia, Widened pulse pressure
- Skin:
  - Warm and moist, "Velvety" texture, ?jaundice
- HEENT:
  - Lid lag and/or stare, Exopthalmos (Graves dz)
- Neck:
  - Goiter or nodule, Bruit
- Cardiac:
  - Tachycardia, hyperdynamic, ?A-fib
- Abdomen:
  - Hyperactive bowel sounds
- Extremities
  - Tremor, hyperreflexic, weakness



Hyperthyroidism vs. Thyroid Storm

It's not the numbers, it's the symptoms! (evidence for end-organ dysfunction)

Thyroid storm

THIS IS A MEDICAL EMERGENCY!!

- **Symptoms (exaggerated) include**
  - **Tachycardia (>140), high output cardiac failure and eventual circulatory collapse**
  - **Hyperthermia (>104 degrees)**
  - **Psychosis or Comatose state (CNS signs)**
  - **GI-hepatic dysfunction**
- **Mortality still 20-75%**
- **Numbers may not be much different from other thyrotoxic patients, so diagnosis is clinical**

Diagnostic criteria for thyroid storm*

Thermoregulatory dysfunction		**Cardiovascular dysfunction**	
Temperature		Tachycardia	
99-99.9	5	99-109	5
100-100.9	10	110-119	10
101-101.9	15	120-129	15
102-102.9	20	130-139	20
103-103.9	25	>140	25
> 104	30	**Congestive heart failure**	
Central nervous system effects		Mild	
Mild		Pedal edema	5
Agitation	10	Moderate	10
Moderate		Bibasilar rales	
Delirium		Severe	
Psychosis		Pulmonary edema	15
Extreme lethargy	20	Atrial fibrillation	10
Severe		Precipitant history	
Seizure		Negative	0
Coma	30	Positive	10
Gastrointestinal-hepatic dysfunction			
Moderate			
Diarrhea			
Nausea/vomiting			
Abdominal pain	10		
Severe	20		
Unexplained jaundice			

>45: Storm likely
25-45: Pending storm
<25: Storm very unlikely
Sensitive but not specific

From Burch and Wartofsky, 1993

Thyroid Storm

- Often associated with a precipitating factor:
  - Long-standing untreated hyperthyroidism (ie. Graves)
  - Thyroidal or non-thyroidal surgery
  - Trauma
  - Infection or other body stressor
  - Acute iodine load (CT scan) (Jod-Basedow effect)
  - Medication related
    - Lithium
    - Amiodarone
  - Rare: Struma ovarii, hCG-secreting tumors

Treatment of thyroid storm

- Supportive care
  - Cardiopulmonary support as needed
  - Cooling, acetaminophen
  - Fluids, calories and vitamins

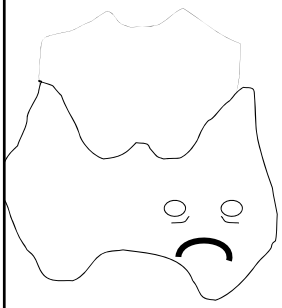
Treatment of thyroid storm

- Acute treatment to lower T4 and control HR
  - Beta-blockers (Propranolol 60 mg every 4-6 hours) immediately
  - Start Thionamides ASAP – PTU 200 mg q4hrs
    - Emergent thyroidectomy if contraindication
  - SSKI, Lugol's, ipodate po.
    - Delay 1 hour after thionamides – prevent iodine from being used as substrate for new hormone synthesis
    - Massive doses of free iodide inhibit organification (Wolff-Chaikoff effect)
  - Glucocorticoids (Hydrocort 100 mg IV q8hrs) also may be helpful
  - Dialysis or plasmapheresis as last resort

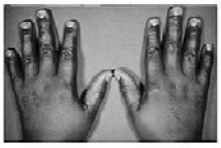
Hypothyroidism and Myxedema Coma

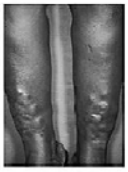
It's not the numbers, it's the symptoms!
(evidence for end-organ dysfunction)
(again)

Myxedema Coma



- Coma or decreased mental status
- Hypothermia
- Bradycardia
- Hypotension and Narrowed pulse Pressure
- Hypoventilation
- Hyponatremia
- Hypoglycemia
- Delayed reflexes
- Pericardial effusion
- Myxedema (Mucin deposits)





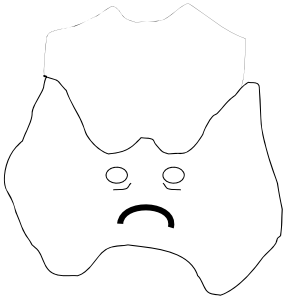
Author: Herbert L. Fred, MD and Hendrik A. van Dijk

2000

When to suspect myxedema?

- Usually insidious onset
- Unable to wean patient from ventilator
- Decreased mental status for no apparent reason (especially in nursing home or isolated patients)
  - ? Not getting L-T4
- Meds
  - Amiodarone
  - Lithium

Myxedema Coma



- L-thyroxine (T4) IV
  - 200-400 mcg IV x1
  - then 1.6 mcg/kg mcg daily
- triiodothyronine (T3) IV
  - 5-20 mcg x1
  - Then 5-10 mcg q8h
- Corticosteroid IV
  - Stress dose Hydrocortisone or Dexamethasone (until you're sure not adrenal insufficient)
- Supportive measures
  - Warming Blanket
- Unfortunately, mortality high (30-40%)