Brigham and Women's Hospital
Founding Member, Mass General Brigham

Adrenal and Thyroid Topics in Hospital Medicine

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures

Alexion Pharmaceuticals:

- Site PI for Global Hypophosphatasia Registry
- Site PI for multi-institutional enzyme replacement clinical trial

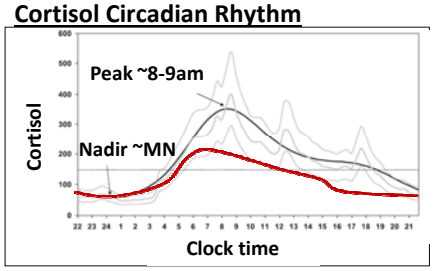
Adrenal & Thyroid

- Adrenal Insufficiency
  - Primary vs Secondary
  - Glucocorticoid dosing
- Adrenal nodules
- Work-up for excess adrenal hormone production
  - Cortisol
  - Aldosterone
  - Catecholamines
- TFT interpretation in hospitalized patients
  - Sick euthyroid/Non-thyroidal illness
- Hyperthyroidism
  - Special circumstances
  - Treatment
- Hypothyroidism
  - Special circumstances
  - Treatment

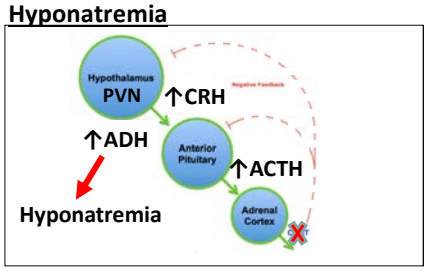
Adrenal Insufficiency

- Signs and Symptoms
  - Weakness, fatigue, anorexia
  - Weight loss, nausea/vomiting, abd pain
  - Orthostatic hypotension
  - Myalgias, arthralgias
  - Fever, eosinophilia, hyponatremia

Cortisol Circadian Rhythm



Hyponatremia

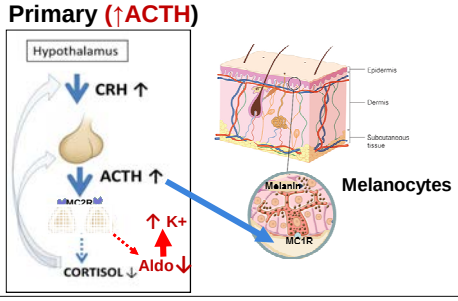


Primary vs Central AI

Primary AI Only

- ↑ pigmentation (↑ACTH)
- ↑K+, acidosis (↓ Aldo)
- **Autoimmune,** infx, vasc, surgery
- Other autoimmune d/o (Hashimoto's, vitiligo, T1DM, etc.)

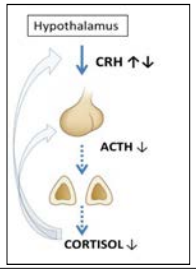
Primary (↑ACTH)



Central AI Only

- **Glucocorticoid w/d**
- **Immune check-point inhibitors**
- Hypothalamic/pituitary d/o
  - Pituitary dysfunction
    - **Central hypothyroidism, hypogonadism, hyperprolactinemia**
    - **Diabetes Insipidus**
  - Mass effect

Central (↓ACTH)



Adrenal Crisis

- In ~ 40% of pts w chronic AI (1^o > central)
- Triggered by acute event
  - Infection, trauma, acute illness, stress, ↑T4
- Signs and symptoms
  - Hypotension/Shock
    - ↓ Vascular tone ± volume depletion
  - Delirium, psychosis, cognitive defect
  - GI Sx ("Acute Abdomen")
  - Fever, hypoglycemia, hyponatremia

From Addison's Original Series 1855

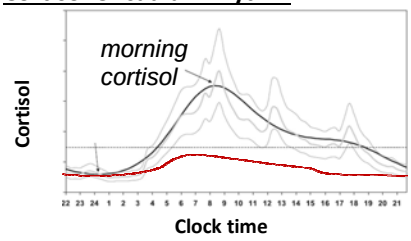
Leelarathna. QJM 2009

Charmandari.Lancet.2015.

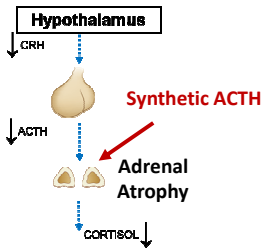
Testing for Adrenal Insufficiency

- **Morning Cortisol** (6-9 am)
  - ≥ 14 ug/dL rules out; <3 ug/dl is suggestive
  - Random cortisol is often indeterminate
    - Useful in suspected adrenal crisis prior to trx

Cortisol Circadian Rhythm



- **Cosyntropin stimulation test (250 ug)**
  - Can be done at any time of day (test for adrenal atrophy)
  - Abnormal if 1hr post ACTH cortisol < 14* ug/dL [*=depends on assay]
    - Dexamethasone does not interfere w cortisol assay
    - May be falsely normal in acute central AI or if ↑ CBG
    - May be falsely abnormal if low CBG (low albumin)

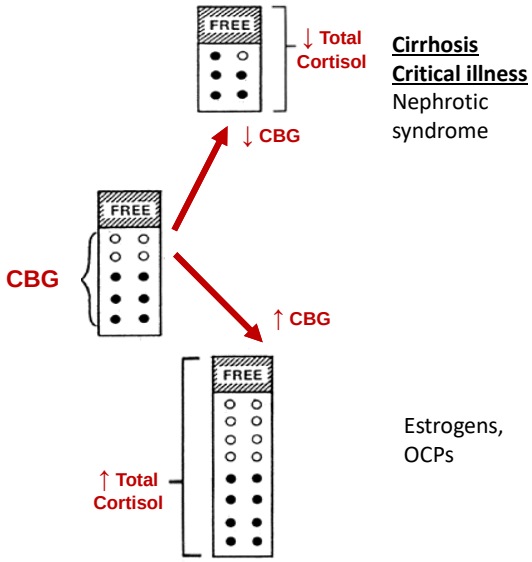


- *Insulin Tolerance Test (Gold Standard) or metyrapone test*
  - *Assess entire HPA axis but seldom used*

Kumar.Postgrad Med J.2022
Coluzzi. Int J Mol Sci.2023.

Cortisol in the Circulation

- > 90% cortisol is protein-bound
  - CBG - 60-75%
  - Albumin – 15-25%
- Only free cortisol is biologically active
- ΔCBG →Δ Total cortisol



El-Farhan.Clin Endo.2013

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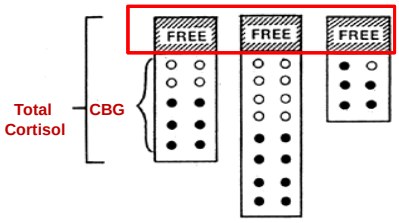


↑CBG
- Estrogens (OCP)
- Chronic active hepatitis
- Genetic variants

↓ CBG
- **Cirrhosis**
- Fever, ↑ T4, **Critically ill**
- Nephrotic syndrome
- Genetic variant

Qualitative "Adjust" Cortisol Values if Albumin ≤ 2.5 g/dL

Hamrahian.NEJM.2004

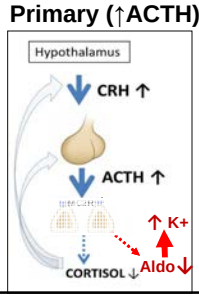
Primary vs Central AI

INCREASED ACTH

- ↑ pigmentation (↑ACTH)
- Etiology
  - **Autoimmune**
    - + 21-hydroxylase antibodies
    - Other autoimmune d/o (Hashimoto's, vitiligo, T1DM, etc.)
  - Infection, vasc, surgery

Testing:
- **↑ACTH**
- **↑K+, ↓ Aldo, ↑Renin**
- **↓ DHEAS**

Primary (↑ACTH)

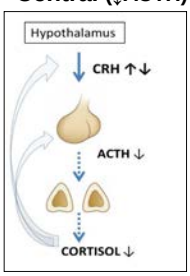


SUPPRESSED ACTH

- Pituitary mass effect (EOM abnl)
- Etiology
  - **Glucocorticoid w/d**
  - **Checkpoint inhibitors**
  - Hypothalamic/pituitary d/o
    - Tumors, infiltrative dz, surgery/XRT

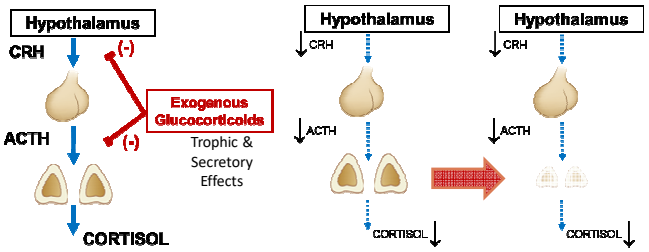
Testing:
- **↓ ACTH**
- **Normal aldo/ renin, K+**
- **↓/Normal DHEAS**
- **Pituitary dysfunction**
  - **Central ↓TSH & ↓T4, DI, etc**

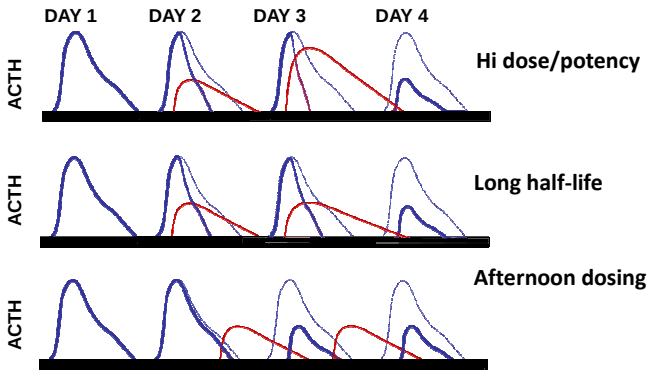
Central (↓ACTH)



Exogenous Steroids

- Suppressed HPA axis
  - High dose, long $t_{1/2}$, pm dosing
  - Long duration
- Likely suppressed HPA axis if:
  - ≥ 20 mg prednisone x >3 wk
  - On steroids & appears cushingnoid
- Suppressed HPA axis **<u>unlikely</u>** if:
  - < 3 wk of steroids
  - Morning prednisone <5 mg





Glucocorticoid Preparations

Compound	MR Activity	GR Activity	Duration of Action (Biologic t ½)	Equivalent Daily Dose (mg)	Special Notes
Hydrocortisone	1	1	S (8-12h)	20	= Cortisol
Cortisone	0.8	0.8	S (8-12h)	25	Needs HSD1
Prednisone	0.8	4	I (12-38h)	5	Needs HSD1
Prednisolone	0.8	4	I (12-38h)	5	Binds CBG
Methyl-prednisolone	0.5	5	I (12-38h)	4	↑Aqu Solubility
Triamcinolone	0	5	I (12-38h)	4	Topical use
Betamethasone	0	25	L (36-72)	0.8	Cross placenta
Dexamethasone	0	25	L (36-72)	0.8	No cortisol assay interference

Merck Manual.2023

Treatment

- Glucocorticoid replacement **BEFORE** T4 replacement
  - Hydrocortisone (~10-12 mg/m^2): 15 mg am/5 mg pm (20/10 in hospitalized pts)
  - Prednisone: ~ 5-10 mg
- Mineralocorticoid replacement for primary adrenal insufficiency
  - Fludrocortisone: 0.05-0.2 mg
  - Not needed if hydrocortisone dose >50 mg/24h
  - Adjust dose based on BP, K+, and renin levels (to upper limits of nl)
- Sick rules
  - "3x3 Rule"- ↑ glucocorticoid dose ~ 2-3x for 3 days
  - Injectable glucocorticoids in case of emergency
  - Medical alert bracelet / Emergency Medical Information Card

Coursin.JAMA.2002; Charmandari.Lancet.2015; Bornstein.JCEM.2016.

Should I Give Stress Doses?

- Stress doses
  - Minor (endoscopy)- 25 mg hydrocortisone (HC) on day of procedure
  - Moderate (ortho)- 50 -75 mg HC on day of surgery and first post-op day
  - Major (CABG) – 100 mg HC prior to procedure, 50 mg HC q 8-12h for 2-3 days

- Hospitalized patient with fatigue
  - 2 mg q 6 dexamethasone= Prednisone 50 = Hydrocortisone 200
  - 15 mg of prednisone = Hydrocortisone 60
  - √ 15 /5 mg hydrocortisone
  - √ Stopped 2 week course of 8 mg dexamethasone 5 days ago

Borstein.JCEM.2016

Common Steroid Equivalences

- Glucocorticoid activity
  - Maintenance dose
- Mineralocorticoid activity
  - Potassium effects

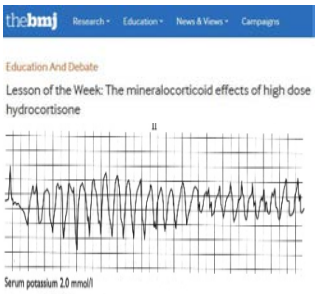
	Glucocorticoid Activity	Mineralcorticoid Activity	Effect Duration (hr)	Equivalent Dose (mg)
Hydrocortisone	1	1	8-12	20
Prednisone	4	0.8	18-24	5
Prednisolone	4	0.8	18-24	5
Methylprednisolone	5	0.5	18-24	4
Dexamethasone	25	0	36-48	0.75

Merck Manual.2023

Lessons in Pharmacology

63 yo M w ETOH cirrhosis p/w GIB and ITP

- INR 1.7, plt 4, initial K+ 3.7
- IVF, Blood & platelet, IV PPI
- IVIG & **<u>IV hydrocort 100 qid x 6 d</u>**
  - K+ 2.6 ->started IV 40 mmol KCL/d
  - K+ 2.9, plt 110
- Stopped KCL supplementation
  - K+ 2.0-> Torsades



Compound	MR Activity	GR Activity	Duration of Action (Biologic t ½)	GR Equiv 400 mg hydro-cortisone	MR Equiv 400 mg hydro-cortisone
Hydrocortisone	1	1	S (8-12h)	400	400
Methyl-prednisolone	0.5	5	I	80	40
Dexamethasone	0	25	L (36-72)	16	0

Ramssahoye.BMJ.1995.

Adrenal Nodule

A 62-year-old woman with 40-pack year smoking history, remote h/o lung CA s/p wedge resection without h/o recurrence and HTN on lisinopril and amlodipine who is admitted with fevers, chills, leukocytosis, and L flank pain. CT of the abdomen reveals left sided pyelonephritis without hydronephrosis and two hypodense adrenal nodules with smooth borders measuring 2.5 cm on the right and 1.5 cm on the left. Serum electrolytes are normal.

Which of the following is the most important indicator of the malignant potential of the adrenal incidentalomas?

A. Size
B. High fat content of the nodules
C. Hormonal status
D. Smooth borders
E. Bilateral involvement

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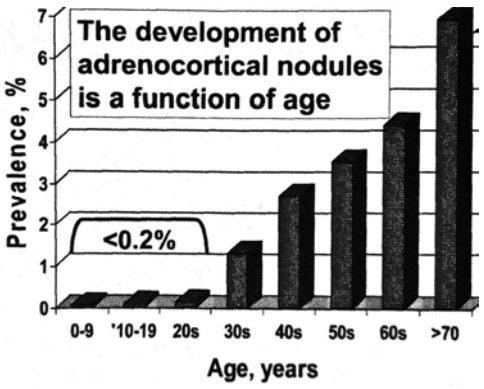
Adrenal "Incidentaloma"

- Adrenal mass >1 cm
- Incidentally discovered during radiographic evaluation
- Increasing in incidence because of widespread use of abdominal imaging

Prevalence of Adrenal Nodules

- Autopsy ~ 6%
  - » Young. 2000
- Abdominal CT ~ 4%
  - » Bovio.2006
- Prevalence ↑ with age
  - – 20-30 yo ~ 0.2%
  - – 40-50 yo ~ 3%
  - – >70 yo ~ 7%
  - » Kloos.1995

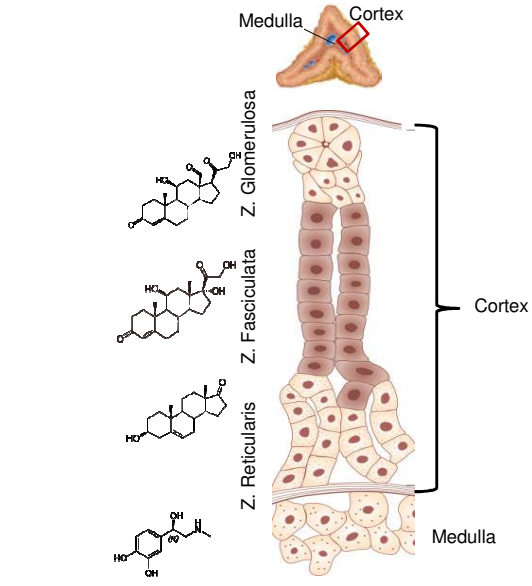


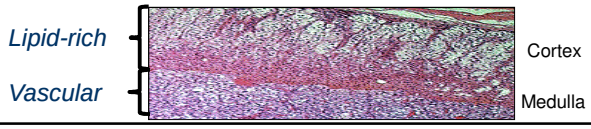
EVALUATION

- IS IT MALIGNANT?
- IS IT FUNCTIONAL?

Adrenal Anatomy

- CORTEX
  - –**Lipid-rich** due to cholesterol based hormones
    - •Glomerulosa – Aldosterone
    - •Fasciculata – Cortisol
    - •Reticularis – DHEA
- MEDULLA
  - –**Lipid-poor & vascular**
    - •Chromaffin- Epinephrine

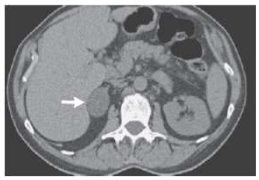




Radiographic Phenotype: Fat Content

- **High fat content = Benign**
  - **CT**
    - **low attenuation (<10 HU)**
    - ***[Rapid washout of contrast (>50% washout in 10', >60% in 15")]***
  - **MRI**
    - **signal loss on out-of-phase images in chemical shift MRI (lipid sensitive mode)**

Adenoma



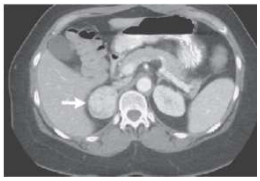
3.6cm

-18 HU

>60% washout

- **Low fat content**
  - **CT**
    - **Increased attenuation (prominent vascularity)**
    - ***[Delayed washout of contrast]***
  - **MRI**
    - **high signal intensity in T2 imaging**

Pheochromocytoma

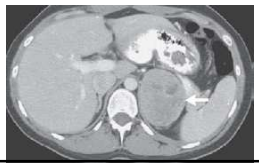


4.5 cm

40 HU

<50% washout

Adrenocortical CA



7.5 cm

30 HU

<50% washout

Kloos.1995, Szolar.2005, Bancos.2021

Predictors of Malignancy

- Cancer history
  - History of cancer (esp. lung, breast, kidney, GI)
    - 20-50% of adrenal masses are mets (can be bilateral)
  - No known cancers
    - >90% represent benign lesions
- Size of Mass (if no h/o CA, >80% metastases <3cm)
  - **<4 cm-** ~ 5% malignant (if no h/o CA)
  - **>6 cm**- ~ 25% malignant
- Radiographic Phenotype

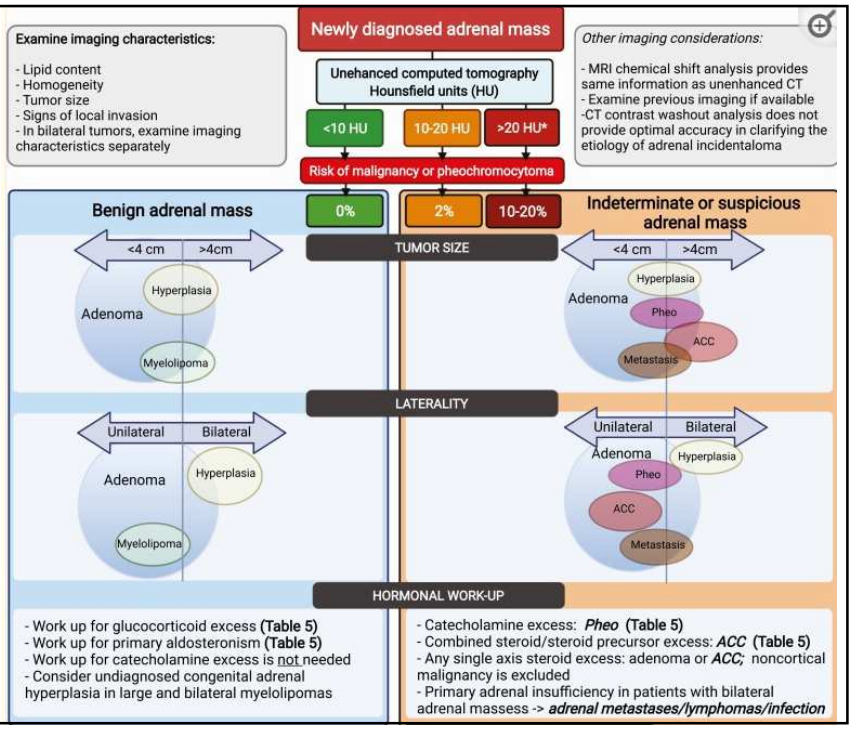
Good	**Bad**
Smooth	Irregular
Homogenous	Heterogeneous (w necrosis, calcification)
<10HU, ↑washout (MRI chemical shift)	> 30 HU, ↓washout (MRI no chemical shift)
Slow growth (<1cm/yr)	Rapid growth (>1cm/yr)
No FDG avidity on PET	↑ FDG avidity on PET

Grumbach.NIH Consensus.2002, Lee. Endo Metab.2016, Vaidya.Endocr Pract.2019, Bancos.JCEM.2021.

Adrenal Incidentaloma

- Lipid content
- Tumor size
- Radiographic phenotype
- Cancer history
- Genetic syndrome

Bancos.JCEM.2021



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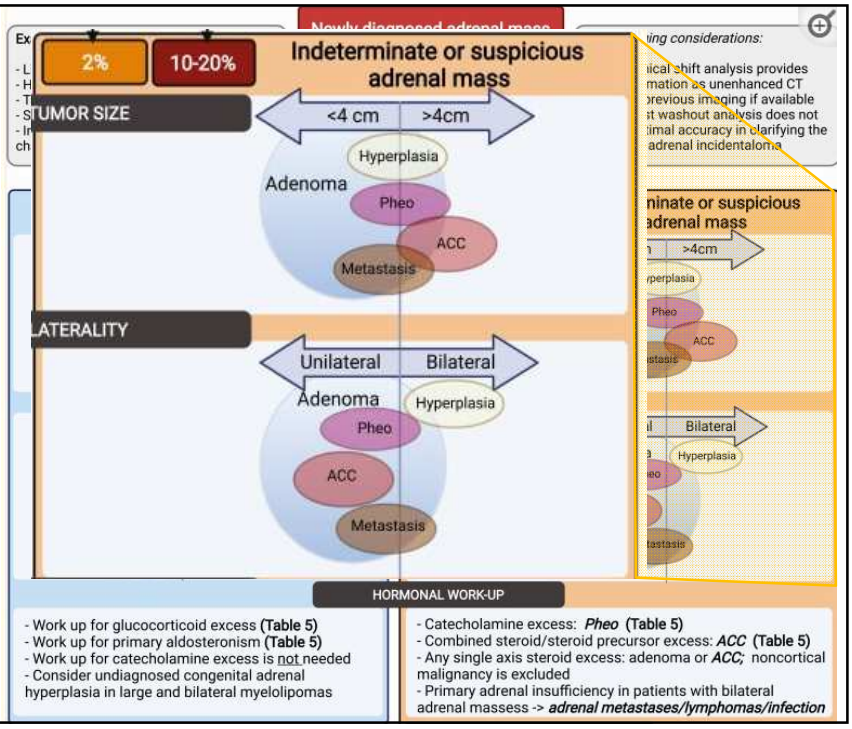
Bancos.JCEM.2021



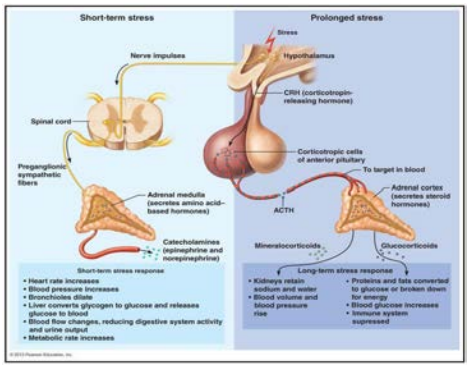
Functional Adrenal Incidentalomas

- Cortisol secreting adenomas
  - ~25% have Mild Autonomous Cortisol Secretion (MACS)
    - Subclinical Cushing's w/o typical findings of hypercortisolemia
  - ~5% with clinical Cushing Syndrome
- Pheochromocytomas
  - ~ 5-10% of adrenal incidentalomas
  - 60% of pheochromocytomas discovered incidentally as adrenal masses
    - Only ~50% of incidentally discovered pheos had HTN
- Aldosterone secreting adenomas
  - ~1-5% of incidentalomas
  - Most with HTN

Young. Endo Metab Clin NA.2000; Bancos.JCEM.2021

Functional Assessment

- History and physical
- Hormonal testing



Outpatient

- Subclinical features
  - High risk of false + hormone testing in hospitalized pts
- Low-mod risk of malignancy
  - Assess growth

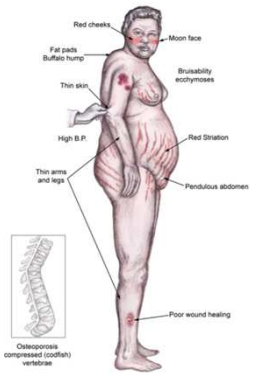
Inpatient

- Severe clinical phenotype
- R/o pheo prior to procedure
- High risk of malignancy
- Other (social, frail, etc.)

When to Test for Adrenal Hormone Excess in Hospitalized Patients

- Evaluation for secondary HTN in hypertensive urgency/emergency if not already done
  - Primary aldosteronism >>> Cushing's or pheo
- Evaluation for pheochromocytoma in patient with lipid-poor incidentaloma awaiting surgical procedure
  - Most patients with pheos don't have spells or uncontrolled HTN
- Suggestive clinical syndromes
  - Cushingnoid or abrupt hypokalemia, hyperglycemia, & HTN in pt with cancer
  - HTN and hypokalemia

Cushing's Syndrome



History and Physical

- Moon facies, plethora
- Central obesity, subclavicular, dorsocervical fat pads
- Depression, emotional lability
- HTN
- Fungal infections
- ***Easy bruising**
- ***Proximal muscle weakness**
- ***Violaceous, wide striae**


vs


Laboratory Findings

- ***Hypokalemia**
- Hyperglycemia/DM
- Leukocytosis with relative lymphopenia
- Osteopenia/osteoporosis

Pheochromocytoma

History and Physical

- **Pounding headaches**
- **Perspiration**
- **Palpitations**
- **Pressure abnormalities**
  - HTN / Orthostasis
- Pallor
- Paroxysmal or persistent spells
- "Phever"/pyrexia
- Plugging= constipation
- **Poor appetite = Anorexia**
- Panic = Anxiety, tremor
- Lid lag

Laboratory Findings

- Hemoconcentration
- Hypercalcemia
- Hyperglycemia

Hyperaldosteronism

History and Physical

- HTN
- +/- symptoms of hypokalemia
  - Muscle weakness / cramping
  - Paresthesias
  - Palpitations
  - Polyuria / polydipsia

Laboratory Findings

- ***Hypokalemia (<35%)**
  - ↓ Insulin → hyperglycemia
- Metabolic alkalosis

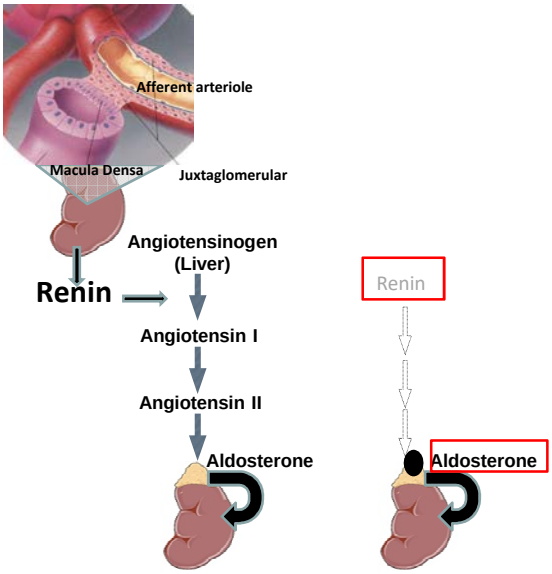
Prevalence

- All HTN – 6%
  - <160/100 -2%
  - <180/110 -8%
  - >180/110 -13%
- Resistant HTN – 20%
- HTN & adrenal nodule – 1-5%
- Increased prevalence in:
  - HTN & ↓K+
  - HTN & OSA
  - HTH in young
  - +FHx of early CVA

Funder.JCEM.2016, Vaidya.Endocr Prac.2017, Auchus.Endocr Prac.2023

Hormonal Testing

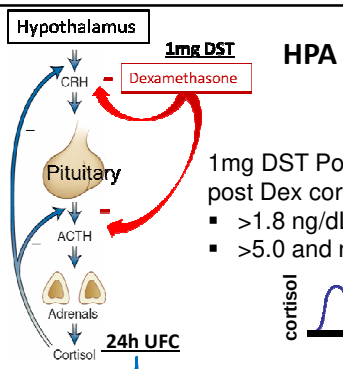
	Prevalence	Initial Testing
Primary Aldosterone	~5% of HTN (~4 Million)	• Aldo:Renin Ratio
Cushing's Syndrome	<1% of HTN (<5K/yr)	• 1mg DST • MN cortisol • 24h UFC
Pheochromo-cytoma	<1% of HTN (<5K/yr)	• Plasma MNPs



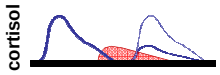
PA screening Positive if:
ARR* >20 **AND** Aldo >8-10 ng/dL
(*-aldo in ng/dL/renin in ng/ml/h)

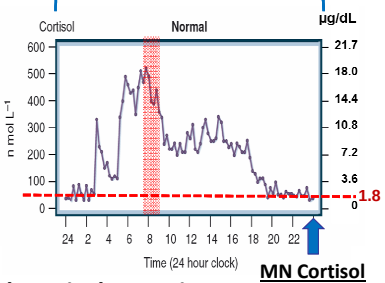
Hormonal Testing

	Prevalence	Initial Testing
Primary Aldosterone	~5% of HTN (~4 Million)	• Aldo:Renin Ratio
Cushing's Syndrome	<1% of HTN (<5K/yr)	• 1mg DST • MN cortisol • 24h UFC
Pheochromo-cytoma	<1% of HTN (<5K/yr)	• Plasma MNPs



1mg DST Positive if post Dex cortisol:
- >1.8 ng/dL and Cushingoid
- >5.0 and not Cushingoid

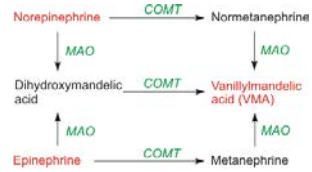


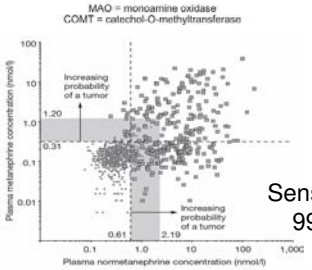


Diurnal Cortisol Secretion

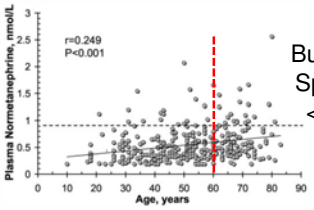
Hormonal Testing

	Prevalence	Initial Testing
Primary Aldosterone	~5% of HTN (~4 Million)	• Aldo:Renin Ratio
Cushing's Syndrome	<1% of HTN (<5K/yr)	• 1mg DST • MN cortisol • 24h UFC
Pheochromo-cytoma	<1% of HTN (<5K/yr)	• Plasma MNPs





Sensitive 99%



But NOT Specific <80%

Sawka.JCEM.2003; Lenders.JCEM.2014, Bancos.JCEM.2021

Hormonal Testing

Medical Mgt

	Prevalence	Initial Testing	Confirm / Localizing Tests	Disease Distribution
Primary Aldosterone	~5% of HTN (~4 Million)	• Aldo:Renin Ratio	• IV saline suppression ❖ AVS	• 70% bilat • 30% uni
Cushing's Syndrome	<1% of HTN (<5K/yr)	• 1mg DST • MN cortisol • 24h UFC	• MN cortisol • 1mg DST • 24h UFC ❖ ACTH ❖ Dex/CRH ❖ 8mg DST/IPSS	↑ ACTH • 65% Pituitary • 10% Ectopic ↓ ACTH • 25% Adrenal
Pheochromo-cytoma	<1% of HTN (<5K/yr)	• Plasma MNPs	• 24h Urine Metanephs ❖ MIBG ❖ Chrgranin A	• 10% bilat • 90% uni

If Positive → **SURGERY**
(except bilateral aldosteronism)

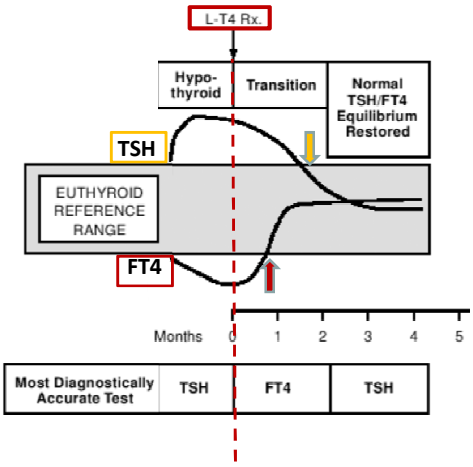
High-Yield Thyroid Topics in Hospital Medicine

- TFT interpretation in dynamic processes
  - Sick-Euthyroid/Non-Thyroidal Illness
  - Iodinated contrasts and the thyroid
- Hyperthyroidism
  - Thyroid storm vs apathetic hyperthyroidism
  - Treatment overview
- Hypothyroidism
  - Central hypothyroidism (glucocorticoid suppression)
  - Treatment, including PO to IV conversion

TFTs: Static View of a Dynamic Process

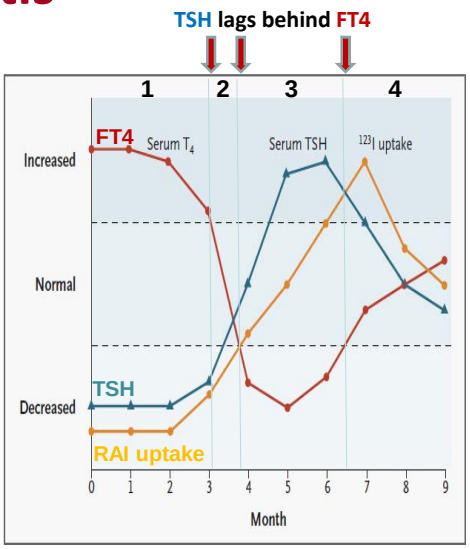
TSH Lags Thyroid Hormone Level

- When correcting thyroid abnormalities, FT4 corrects before TSH
  - Lag depends on
    - Severity
    - Duration of abnormality
- Days-weeks time scale is more common in hospitalized patients
- TSH is indicative of baseline fnx, but thyroid hormone levels better for assessing change
  - Hypothyroidism Tx- follow FT4
  - Hyperthyroidism Tx- follow T3 & FT4
    - TSH can remain suppressed for months



Thyroiditis

- Multiple etiologies
  - Autoimmune (+TPO, nl ESR)
    - Painless sporadic
    - Post-partum
    - Hashimoto's
    - **Immune check-point inhibitors** (-TPO)
  - Destructive
    - Painful subacute **(↑ ESR)**
    - Drug-induced
    - *Rare - Suppurative*
      - Riedel's
- Multiple stages/transitions
  1. Thyrotoxic
  2. Euthyroid
  3. Hypothyroid
  4. +/- Recovery

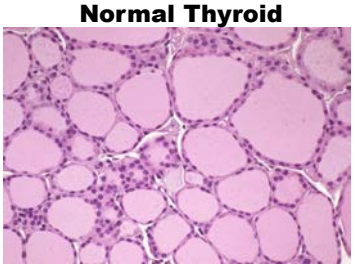


Pearce.NEJM.2003; Samuels. Med Clin North Am.2012

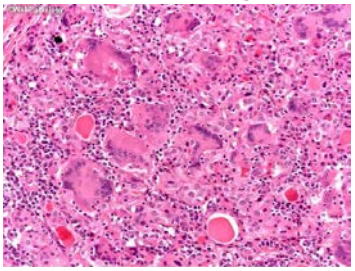
Treatment

- Thyrotoxic stage
  - Beta Blocker
    - 60 mg propranolol LA/d
  - **NSAIDS** vs prednisone
    - 500 mg naproxen bid
    - 40 mg prednisone (if severe)
  - NOT THIONAMIDES!
- Hypothyroidism
  - Transient- post viral/painless sporadic
    - LT4 not often needed
    - Consider 6-8wks if severe
  - Permanent- ICI
    - Need permanent replacement

Normal Thyroid



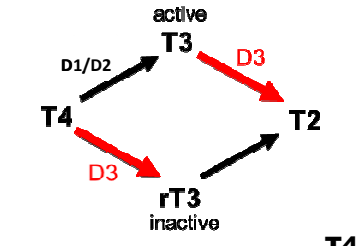
Granulomatous Thyroiditis

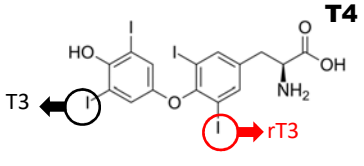


Non-Thyroidal Illness

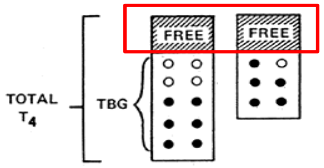
AKA: Sick Euthyroid= Low T3 Syndrome = D3 Syndrome

- **Increased D3 Activity**
  - ↑rT3 (inactive), ↓ T3





- **Decreased TBG**
  - ↓Total T4
  - No change in FT4



Non-Thyroidal Illness

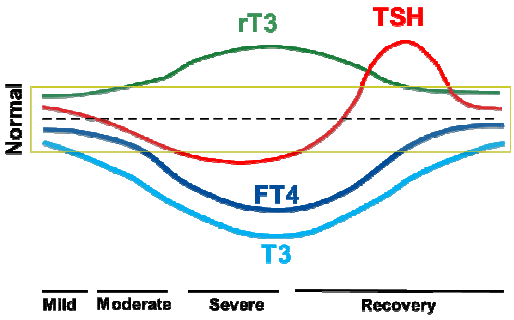
- Illness (mild → moderate → severe)
  - ↑D3 & ↓D2 activity
    - ↑ rT3 & ↓T3
  - ↓ TBG
    - ↓Total T4 & T3
  - ↓ TRH → ↓ TSH
    - ↓ FT4
    - TSH usually not undetectable
- Recovery → ↑ TSH
  - TSH usually **NOT** > 25 uU/mL
- Multiple mechanisms
- LT4 treatment not helpful

	Mild	Moderate	Severe	Recovery
Example	Viral Illness	Pna	ARDS	Wards
TSH	-	-, ↓	↓↓	↑
FT4	-	-	↓	↓
T4	-	↓	↓↓	↓
T3	↓	↓↓	↓↓	↓↓
rT3	↑	↑↑	↑↑↑	↑↑
TBG	-	↓	↓↓	↓

Boonen.JCEM.2014; Fliers.J Endo Invest.2021

Non-Thyroidal Illness

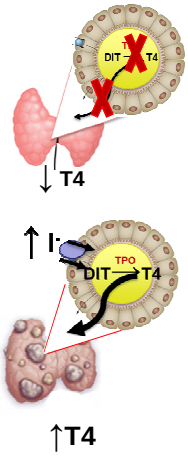
- Illness (mild → moderate → severe)
  - ↑D3 & ↓D2 activity
    - ↑ rT3 & ↓T3
  - ↓ TBG
    - ↓Total T4 & T3
  - ↓ TRH → ↓ TSH
    - ↓ FT4
    - TSH usually not undetectable
- Recovery → ↑ TSH
  - TSH usually **NOT** > 25 uU/mL
- Multiple mechanisms
- LT4 treatment not helpful



Boonen.JCEM.2014; Fliers.J Endo Invest.2021

Iodine and Thyroid

- Iodine
  - Wolff-Chaikoff
    - Iodine inhibits thyroid hormone (TH) formation and release
    - Transient decrease in TH, then escape of inhibition
    - Sustained TH inhibition in autoimmune thyroid dz (+anti-TPO)
  - Jod-Basedow ("Fuel to Fire")
    - Iodine mediated increased in TH formation
    - Usually in pts with MNG or autonomous adenoma (± Graves')
- Amiodarone (~ 7 mg free iodine/200 mg dose)
  - Hypothyroidism ~ 10%
  - Hyperthyroidism ~3% (*but up to 20% in iodine deficient areas*)
    - Type 1 - Jod-Basedow
      - If autonomous tissue, U/S w ↑ blood flow → Tx: methimazole
    - Type 2 – Thyroiditis
      - Release of preformed TH, U/S w ↓ blood flow → Tx: prednisone
  - No need to stop amiodarone given long $t_{½}$ (~60d)

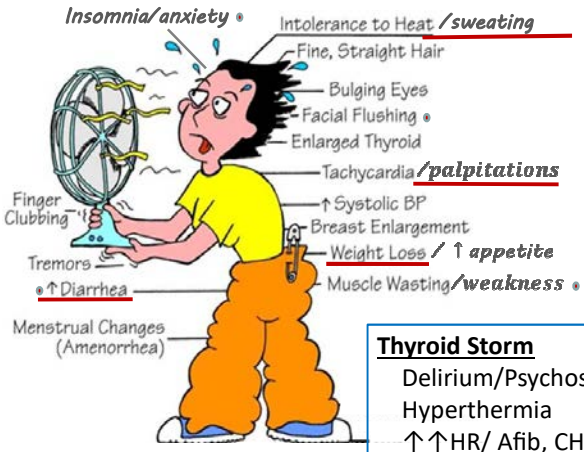


Basaria .Am J Med.2005; Robuschi.J Endo Invest.1986; Chopra.JCEM.1975; Cooper.Am J Med 1982, Lee.JCEM.2015

Hyperthyroidism

Signs
↑HR, Atrial fibrillation
↑SBP
Warm, moist skin
Goiter ± **bruit**
Proptosis (Graves')
Pretibial myxedema

Apathetic thyrotoxicosis
Elderly
↓ Adrenergic Sx
↑ Lethargy/depression



Thyroid Storm
Delirium/Psychosis
Hyperthermia
↑↑HR/ Afib, CHF
GI Sx, ↑ LFTs

Cooper.Lancet.2003; Franklyn.Lancet.2012; Wu.Pathobiology.2010

Thyroid Storm

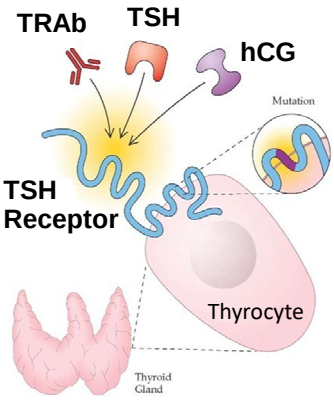
- Incidence- 1-2% of hospitalized pts w ↑FT4/T3
  - Mortality 10-30%
- Altered mental status (agitation, delirium, stupor)
  - **More severe signs & symptoms**
    - Hyperpyrexia (>104); ↑↑HR, arrhythmia, CHF
    - GI (n/v/diarrhea/pain), ↑LFT
  - Precipitants
    - Surgery, trauma, infection, iodine load, parturition, antithyroid med w/d
  - Degree of T4/T3 elevation is not a criterion for dx

Criteria	**Burch & Wartosfky:**	**Akamizu:**
	▪ Likely ≥45 ▪ Impending 25-44 ▪ Unlikely <25	▪ Definitive vs possible ▪ Combination of Sx ▪ **CNS**, fever, tachycardia, CHF, GI/hepatic manifestations

Bahn.Thyroid.2011; Klubo-Gwiedzinska.MedClinNAm.2012; Akamizu.Thyroid.2012; Angell.JCEM.2015

Thyrotoxicosis

- Etiology
  - Graves'=Autoimmune
  - Autonomous nodule(s)
  - Thyroiditis
  - Factitious/iatrogenic
  - Rare (TSH secreting adenoma, germ cell tumors, thyroid hormone resistance, struma ovarii)
- Evaluation
  - Thyroid Receptor Antibodies (TRAb)
    - Thyrotropin Binding Inhibiting Immunoglobulin (TBII)
    - Thyroid-Stimulating Immunoglobulin (TSI)
    - ~95% Sensitivity & specificity
  - RAI uptake & scan



Tozzoli.Autoimm Rev.2012; Barbersino.JCEM.2013

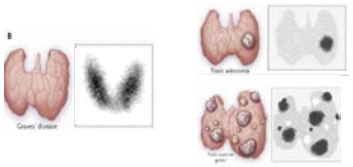
RAI Uptake/Thyroid Scan (contraindicated in pregnancy)

Iodine uptake driven by TSH receptor activity

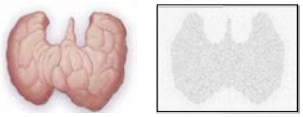
- TSH, auto-antibodies, hCG; autonomous

RAI: 40% uptake (nl 10-30%)

- Increased Uptake
  - Graves' disease
  - Multinodular goiter
  - Toxic adenoma
  - *Rare:*
    - *hCG mediated (GCT, GTD)*
    - *TSH secreting adenoma*
    - *Thyroid hormone resistance*



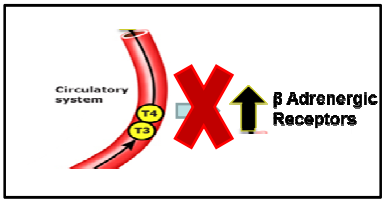
- Decreased Uptake
  - Thyroiditis
  - Factitious/iatrogenic
  - Iodine induced
  - *Rare:*
    - *Thyroid hormone secreting tumors (follicular CA mets/ struma ovarii)*

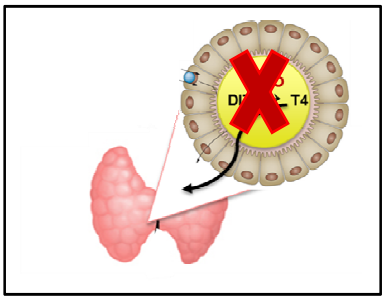


Ross.NEJM.2011, Ross.Thyroid.2016.

Treatment

- Beta Blockers
- Thionamides
  - Methimazole vs PTU
  - Temporizing measures
  - Induce remission (25-75%)
    - Depend on severity, goiter size, & TRAb status
- Radioiodine
- Surgery





Thionamides

	Methimazole	PTU
Mechanism of Action	**Inhibit production** of **NEW** thyroid hormone	
Half –life	6 hr	1.5 hr
Typical /Maintenance dose	15-30 mg / 5-10 mg	100-200 tid/ 50-100 bid
Side Effects	Rash, agranulocytosis, ANCA+ vasculitis (> w PTU)	
Liver toxicity	Cholestasis	Fulminant necrosis
Cross placenta?	Yes	Yes
Pregnancy complications	1st trimester- choanal/ esophageal atresia, omphalocele 2nd & 3rd – aplasia cutis	1st trimester- face/neck cysts, hydronephrosis, genitourinary defects 2nd & 3rd- Liver failure
When preferred?	Most cases	1st trimester, **thyroid storm**

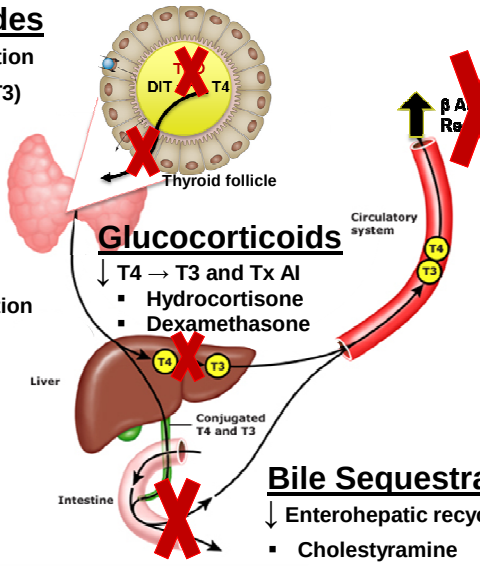
Treatment

Thionamides

↓ New T4 formation
- PTU (↓ T4→T3)
- MMZ

Iodine

↓ T4 Release
- SSKI
- Lugol's solution



Glucocorticoids

↓ T4 → T3 and Tx AI
- Hydrocortisone
- Dexamethasone

β Blockers

↓ Adrenergic tone
(Propranolol ↓ T4 →T3)

Bile Sequestrant

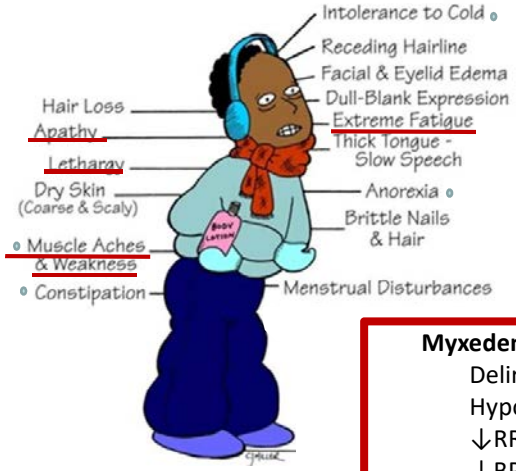
↓ Enterohepatic recycling
- Cholestyramine

Follow FT4 & T3 as TSH can remain suppressed for weeks

Bahn.Thyroid.2011; Klubo-Gwiedzinska.MedClinNAm.2012

Hypothyroidism: Signs & symptoms

Signs:
↓DTR,
hoarseness,
thinning eyebrows,
non-pitting edema,
effusions,
↓HR, ↑DBP,
↓Na, ↑cholesterol,
anemia
↑Prolactin

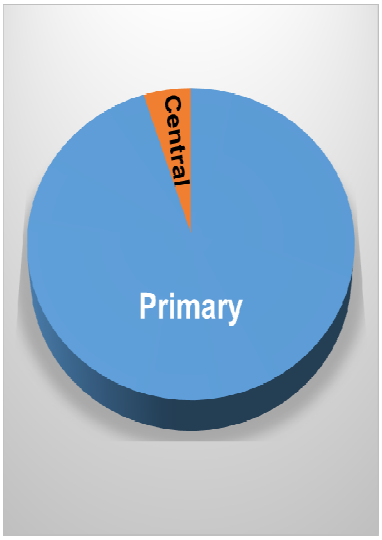


Myxedema Coma/Madness:
Delirium
Hypothermia
↓RR (hypercapnia)
↓BP

Roberts.Lancet.2004; Chaker. Nat Rev Dis Primers.2022

Causes

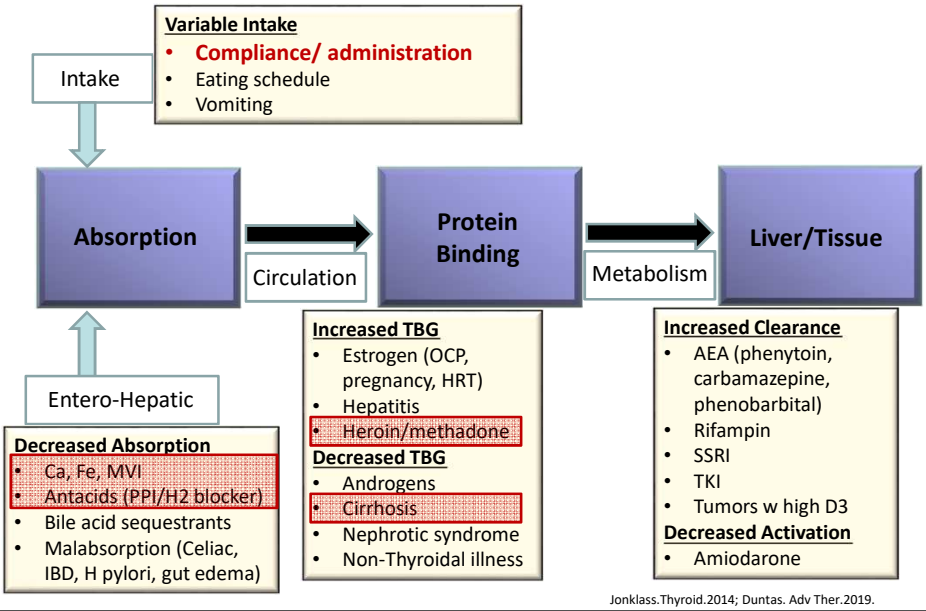
- Primary (↑TSH)
  - Autoimmune (Hashimoto's Thyroiditis)
  - Iodine deficiency
  - Iatrogenic
    - Surgery, RAI, XRT
  - Meds
    - Li, chemo Rx (TKI, **checkpoint inhibitors**), amiodarone
  - Congenital
- Central (↓ TSH)
  - Hypothalamic/pituitary do
  - Glucocorticoids



Treatment & Monitoring

- Levothyroxine (LT4)
  - 1.6 µg/Kg (0.6-0.7µg/lb)
    - In elderly: Start low & Go slow
    - Take fasting, hold tube feeds
    - Long t½ (~ 1wk)
  - PO to IV conversion
    - Give 70% of PO dose in IV formulation
  - Check TFTs in ~6 wks to adjust the dose
    - If TSH in normal range, FT4 is unnecessary
    - T3 measurement rarely required

Thyroid Hormone Variability



Jonklass.Thyroid.2014; Duntas. Adv Ther.2019.

Thank You!