ADRENAL INSUFFICIENCY

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Learning Objectives

- Distinguish the clinical and laboratory findings of primary and secondary adrenal insufficiency
- Appropriately use and interpret the results of basal and dynamic tests of adrenal function
- Basic understanding of the controversy in diagnosis and management of adrenal insufficiency of critical illness
- List the drugs that interfere with the hypothalamic-pituitary adrenal axis and cortisol metabolism
Adrenal Anatomy
Cortex consists of 3 different zones
- Zona Glomerulosa - mineralocorticoids
- Zona Fasciculata - cortisol
- Zona Reticularis - sex hormones

Medulla
- Chromaffin cells - metanephrines and catecholamines
Adrenal Insufficiency

Life threatening disorder, arising from disruption of the normal hypothalamic-pituitary-adrenal (HPA) axis regulation of steroidogenesis. Deficient production or action of glucocorticoids and/or mineralocorticoids and occasionally adrenal androgens.

Central/Secondary
Tertiary Adrenal Insufficiency (Hypothalamic)
Secondary Adrenal Insufficiency (Anterior Pituitary)

Primary Adrenal Insufficiency (Adrenal)
First Clue: Clinical Manifestations

- Fatigue
- Weakness
- Anorexia
- Unexplained Weight loss
- Nausea
- Vomiting
- Abdominal Pain
- Diarrhea (can alternate with constipation)
- Hyperpigmentation (Primary Only)
- Dizziness

- Shock
- None provide very good sensitivity or specificity

Very Rarely are AI patients gaining weight unless have other organ failure disease
Second Clue: Routine Laboratory Abnormalities

- **Hyponatremia:** most common in primary & secondary AI
  - Why? GC exert negative feedback on vasopressin secretion and deficiency of cortisol may result in nonosmotic stimulation of vasopressin
  - **unexplained hyponatremia**

- **Hyperkalemia:** due to deficiency of mineralocorticoids but not seen in all primary AI

- **Hypercalcemia**

- **Hypoglycemia** – rare more in secondary

- **Metabolic Acidosis**

- **Lymphocytosis, eosinophilia**
Imaging abnormalities

- **Primary**: bilateral adrenal enlargement or masses particular when enlargement is with the normal contour of the adrenal glands
- **Atrophic adrenals**
  - Secondary: pituitary or sellar mass
- **Calcifications** – tuberculosis
- **Bleeding** - hx of anticoagulation use, malignancy, coagulation disorders
- **Tumors**
- Most times images **cannot rule in or out** the diagnosis and cannot tell if primary or secondary AI.
Causes of Cortisol Deficiency

MOST COMMON IS IATROGENIC

- All exogenously administered glucocorticoids regardless of dose or route of administration may suppress the HPA axis.

- Endogenous cortisol will suppress in 50% of patients who receive intra-articular or oral GC and 5-10% of patients who received inhaled or topical GC.
Causes of AI

- Pituitary or Sellar tumors
- Granulomatous diseases of pituitary or bilateral adrenals
- Autoimmune destruction of Adrenals
- Hypophysitis of Pituitary
- External Beam Radiation to Sella/Pituitary
- Hemorrhage: Bilateral Adrenals, Pituitary Apoplexy, Sheehan’s
- Adrenal Infiltration due to Lymphoma
- Infectious Adrenalitis (TB, Fungal, HIV, Syphilis)
- Metastasis: Pituitary or Bilateral Adrenals
- Surgical Resection: Hypophysectomy or bilateral adrenalectomy
Medications

- **Who is at risk?** Anyone but particularly in individuals with limited pituitary and/or adrenal reserve

- **Mechanism:** Inhibit cortisol biosynthesis-
  - aminoglutethimide (antiepileptic), etomidate (anesthetic-sedative), ketoconazole (antimycotic) and metyrapone

- **Mechanism:** Adrenolytic – Mitotane (DDT derivative)

- **Mechanism:** Drugs that accelerate the metabolism of cortisol and most synthetic glucocorticoids by inducing hepatic CYP3A4 enzyme
  - Phenytoin, barbiturates, and rifampin
Medications

- Opioids: secondary/tertiary; modify ACTH release
- Psychototropic medication – secondary
- Benzodiazepines (alprazolam), atypical antipsychotics (olanzapine, quetiapine) - secondary
- CTLA-4 monoclonal antibody induced hypophysitis (eg ipilimumab) - secondary
- GR antagonist (mifepristone) - primary
Genetic disorders

- Congenital adrenal hyperplasia
- X-linked Adrenoleukodystrophy
- Autoimmune polyglandular syndromes
- ACTH insensitivity (familial glucocorticoid deficiency)
- Adrenal hypoplasia congenita
- Transcription factor defects
Outside of iatrogenic causes, AI is rare.

- Probability of AI is extremely low in the absence of specific clinical features:
  - hyperpigmentation
  - hypotension
  - hypoglycemia
  - vitiligo
  - known pituitary disease
  - weight loss
  - anorexia
Can be used alone to **exclude** all forms of AI in MOST patients

- Cortisol has strong diurnal rhythm
- AM cortisol before 9:00 am is diagnostically useful
- Basal cortisol values < 3-5 ug/dl highly suggestive but not always diagnostic (clinical correlation needed)
- BUT if cortisol drawn at any time of day is > 14 ug/dl is 99% specific for predicting a cortisol increase greater than 18 ug/dl during an ITT
- Basal cortisol values 5-14 ug/dl are inconclusive and require additional testing
Diagnostic Testing- ACTH

- AM ACTH value itself not used to excluded adequate cortisol production
- If cortisol is low < 5ug/dl the ACTH is useful to distinguish etiology of AI
  - Primary AI: ACTH > 100 pg/ml
  - Secondary AI: ACTH < 15-20 pg/ml (or inappropriately low)
Serum Aldosterone & Plasma Renin Activity

- Not deficient in secondary AI
- Only deficient in primary AI (but not always)
- Aldosterone will be low or undetectable in primary AI but only interpretable with an appropriately elevated renin (>2 ng.ml/h)
250 ug Cosyntropin Stimulation Test

- **Indication:** Definitively exclude primary adrenal insufficiency or *longstanding* secondary adrenal insufficiency
- **Protocol:** IV bolus with sampling baseline, 30 min and 60 min
- **Can be done ANYTIME OF DAY**
- **NORMAL:** A peak cortisol at 30-60min of greater than 18 ug/dl
- **Basal cortisol values vary by time of day and clinical status and should never be used as a diagnostic criterion**
- **Aldosterone normally doubles in response to cosyntropin which can be helpful**
- **Delta of 9 ug/dl not required if peak is >18 ug/dl**
Other dynamic testing- recommend endocrine involvement

- 1 ug cosyntropin stimulation test
  - Controversial use
  - Used in diagnosis of secondary AI
- Insulin Tolerance Test
  - GOLD STANDARD TEST for all forms of AI
  - Tests the entire HPA axis
  - Measures the counter regulatory hormone response to hypoglycemia
  - Useful in equivocal cases of other dynamic testing & secondary AI
  - Contraindications to test: seizure disorders, significant cardiovascular disease, inability to verbalize symptoms of hypoglycemia
Finding the Etiology AI is important!

- Primary AI is rare! So etiology should be pursued due to additional consequences of the diagnosis
  - Children look for genetic causes
  - 21- hydroxylase Ab
  - Young men Adrenal X- linked leukodystrophy
21 Hydroxylase Antibody

- Cause of autoimmune Addison's disease
- Should be checked in all cases of primary AI
- Less commonly positive in children or adults > 60 yr. old
- Sensitivity 90% Sensitivity 100% but immunofluorescence technique is less sensitive

- Young male with primary AI and antibody negative check very long chain fatty acids for Adrenal X-linked leukodystrophy
Special Conditions

- **Cortisol Binding Deficiency**
  - Very rare
  - Low serum cortisol 0.5-2 ug/dl
  - Lack features of AI
  - Can be with severe protein def/losing states
Plasma Free Cortisol During CST

- Useful for patients with hypoproteinemina (critical illness, anasarca)
- Pts on oral contraceptives which cause high CBG
- Free cortisol can be measured in saliva or plasma
Other diagnosis

- **Adrenal Fatigue**: Doesn’t exist
- **Relative Adrenal Insufficiency**: according to endocrinologist doesn’t exist, possibly exists in critical care literature
  - Circulating cortisol is about 10% free hormone and 90% bound
  - The affinity of cortisol for the GC receptor is about 0.362 ug/dl
  - So a total serum cortisol of 7 ug/dl is about 0.7 ug/dl free cortisol which is nearly enough to saturate the GC receptor.
  - So during stress even “low” amounts is often enough
Acute Ill Management with AI

- #1 Aggressive volume replacement with normal saline
- #2 Hydrocortisone (solu-cortef) as IV bolus or infusion, IM ok as well if no IV access
- Exact dose not critical just get some in ASAP
- 20mg HC will sufficiently raise serum cortisol concentrations
Acute Management of AI

 Presumed maximal output of hydrocortisone during severe stress is 200-300mg/day
 Doses of 50mg q6 will raise serum cortisol to 40-120mg/dl
 50 mg IV bolus then 25 q6… if shock 50 q6..stay away from 100 q8
 MOST IMPORTANT is to continue the dosing until patient is well then can take oral regimen
Acute Management of AI

- Doses of hydrocortisone greater than 40mg/dl per day also have a mineralocorticoid effect so do not need fludrocortisone replacement
- If use solumedrol or dexamethasone, need to give florinef
- Pts promptly respond to the first dose of hydrocortisone
Adrenal Insufficiency in the ICU patient with no known previous diagnosis

- Many studies have serious limitations and conflicting results
- NO definitive cut off values, must have clinical correlation
- Most studies did not account for hypoproteinemia which reduces plasma cortisol binding thus higher serum free cortisol to total cortisol concentration
Normal HPA Axis in Critical Illness

- Persistent Hypercortisolemia often 7-10 fold increase in serum free cortisol levels
- Due to the decrease in clearance from the inhibition of 11BHSD2 in the kidney that converts active cortisol to inactive cortisone.
- Neutrophil elastase cleaves liganded CBG releasing cortisol to sites of inflammation
Case findings for partial AI

*Look at clinical setting and prior history for risk factors*

- Prior history of GC or drugs that have GC affect
  - Megace
  - Etomidate (decrease secretion by inhibiting 11 B hydroxylase enzyme, effect can last up to 24hrs)
- Personal or family hx of autoimmune illness
- Known hypothalamic/pituitary illness
- Hx brain irradiation
Diagnostic Testing

- If patient has near normal serum binding proteins (albumin > 2.5 g/dl) then total cortisol in critical illness is reliable
  - Albumin > 2.5 g/dl, Total cortisol ≥ 14-15 ug/dl are expected in critical illness
- If patient has low serum binding proteins (albumin < 2.5 g/dl) then total cortisol in critical illness is not reliable
  - If albumin < 2.5 ug/dl, Total cortisol ≥ 7-11 ug/dl are expected in critical illness
ACTH Stimulation Test in AI During Critical Illness

- Often does not provide any additional meaningful information when accounting for possible delay in care
- If test is performed, must interpret in context!
  - The total cortisol as it corresponds to the protein level
  - The stimulated cortisol will be exaggerated as compared to the ambulatory patient
  - The delta of 7-9 should not be a criterion for defining normal or abnormal adrenal function but can correlated to potential response to HC
  - Normal is peak cortisol at 30-60 min >18 ug/dl
  - Test may be “normal” if AI is secondary and of recent onset which does not allow enough time for adrenal atrophy
• ACTH, Aldosterone, Renin not diagnostically helpful in critical illness
  • Disconnect between acth and cortisol due to impaired cortisol clearance
  • Changes in sensitivity of ACTH to its receptor
  • Changes post translation processing of ACTH
  • Aldo and renin levels can decrease in prolonged serious illness reason unknown
• Consider DHEA-s measurement (which would be low) in AI… if < 65 y/o… takes time to come back
  ▪ Random serum free cortisol expected to be > 1.8 ug/dl in most critically ill patients
    □ Very reliable
    □ Not routinely commercially available
    □ Can take 1 week to come back
Partial Adrenal Insufficiency

- Diagnosis in the outpatient setting is difficult which makes the diagnosis in critical illness even more challenging
- Usually presumption is that patient has enough cortisol reserve for normal daily life but may not have enough reserve at times of severe physiologic stress
- Not necessarily picked up by acth stim test
The routine use of GC during critical illness is not justified except when AI is properly diagnosed or in others who are hypotensive, septic and unresponsive to standard therapy.

Give HYDROCORTISONE at the LOWEST DOSE for the SHORTEST period of time.

Hydrocortisone should be tapered and discontinued as clinically indicated in those who receive the drug without definitive diagnosis to avoid iatrogenic HPA suppression.

Presume you are treating the underlying illness and not AI.
Chronic GC replacement

- 10mg/ m2 (BSA)
- Usually 15-20mg divided into 2 or 3 doses
- Dose to match the normal diurnal rhythm
- Two peaks of cortisol 7am and 8pm
  BID regimen with hydrocortisone
  - 1st dose upon awakening or 30 min prior to arising
  - Next dose 8hrs later and before 6pm
  - TID regimen as well
  - Less preferred is prednisone and dexamethasone since they are long acting and need to be metabolized in the liver to the active hormone
  - Florinef- ONLY In primary AI usually 0.05-0.2mg/day suffices
    - Watch K and BP
SICK DAY rules

- High fever, diarrhea, vomiting: double or rarely triple dose until completely well for 1 day then resume normal dose
- If cannot take meds orally, given IM hydrocortisone shot (should always have) and go to ER
- Planned surgeries: 50 mg IV x once prior to induction of anesthesia for surgeries < 4hrs
- Routine outpatient procedures: double the dose morning of procedure
Treatment

- Treatment of adrenal insufficiency should be initiated as soon as the diagnosis is confirmed, or even sooner if the patient presents in adrenal crisis.
- Patients with primary adrenal insufficiency require life-long glucocorticoid and mineralocorticoid replacement therapy.
# Corticosteroid Comparison Chart

<table>
<thead>
<tr>
<th>Equivalent Glucocorticoid Dose (mg)</th>
<th>Potency relative to Hydrocortisone</th>
<th>Half-Life</th>
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<td>Anti-Inflammatory</td>
<td>Mineral-Corticoid</td>
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### Short Acting
- **Hydrocortisone** (Cortef, Cortisol)
  - 20 mg
  - 1
  - 1
  - 90
  - 8-12
- Cortisone Acetate
  - 25 mg
  - 0.8
  - 0.8
  - 30
  - 8-12

### Intermediate Acting
- Prednisone
  - 5 mg
  - 4
  - 0.8
  - 60
  - 12-36
- Prednisolone
  - 5 mg
  - 4
  - 0.8
  - 200
  - 12-36
- Triamcinolone
  - 4 mg
  - 5
  - 0
  - 300
  - 12-36
- Methylprednisolone
  - 4 mg
  - 5
  - 0.5
  - 180
  - 12-36

### Long Acting
- Dexamethasone
  - 0.75 mg
  - 30
  - 0
  - 200
  - 36-54
- Betamethasone
  - 0.6 mg
  - 30
  - 0
  - 300
  - 36-54

### Mineralocorticoid
- Fludrocortisone
  - 0 mg
  - 15
  - 150
  - 240
  - 24-36
- Aldosterone
  - 0 mg
  - 0
  - 400 +
  - 20
  - -


### Commonly Prescribed Replacement Steroid Equivalents

- Prednisone
  - 5 mg = 25 mg = 0.75 mg = 20 mg

- Cortisone
Case 1

- Asked to see pt regarding diagnosis of adrenal fatigue in 19 y/o man complaining of panic attacks accompanied by palpitations and weakness.
- Diagnosis of adrenal fatigue made by a salivary cortisol profile.
- Pt’s mother at the visit
PE

- Healthy male
- Normal skin pigmentation
- 124/74 HR 60
- BMI 21
- PE=normal
- Early morning cortisol 1.2 ug/dl
Which of the following tests would you obtain next?

- A. Plasma ACTH
- B. 250 ug ACTH stimulation test
- C. Pituitary MRI
- D. DHEA-S
Results

- 250 ug Stim test was done and peak cortisol was 11.6 ug/dl
- Basal ACTH < 5
- Total T, Free T4, IGF-1 wnl
- Which of the following studies would you get next?
  - A. Pituitary MRI
  - B. ITT
  - C. 1 ug cosyntropin stimulation test
  - D. Renin level
- Pituitary MRI is normal
- Which of the following studies would you get next?
- A. Measurement of long chain fatty acids
- B. 21 Hydroxylase antibodies
- C. Synthetic glucocorticoid screen
- D. 17 Hydroxyprogestone (Congenital Adrenal hyperplasia)
- Synthetic GC screen negative
- Two weeks after the initial visit, the patient’s mother calls you and finds what in his drawer?
  - Opioid
    - Does he really have adrenal insufficiency
    - Should you treat
Case 2

- 73 y/o man with T2DM was admitted with lobar pneumonia diagnosed 6 days prior. During the last 36 hrs he developed fever, hypotension, and decreased urine output and transferred to the ICU requiring intubation, mechanical ventilation and sedation.

- He receive aggressive isotonic fluid resuscitation, BS antibiotics and IV insulin.

- Na, K wnl Glucose controlled

- Calcium 7.9 mg/dl

- Albumin 1.9 mg/dl
- Intensivist performed assessment of adrenal function
- Basal serum cortisol was 11ug/dl
- 250 mcg acth stim test peak cortisol 17.5 ug/dl, increment of 6.5 ug/dl
- Serum aldosterone 3.5 ug/dl
- Plasma renin activity 12 ng/mg/h
- Basal Plasma ACTH 17 pg/ml
Does he have adrenal insufficiency based on laboratory evaluation?

- Partial Adrenal Insufficiency
- AI of critical illness
- Relative Adrenal Insufficiency
- Primary AI
- Secondary AI
Which of the following tests would you do next?

A. Administer hydrocortisone with fludrocortisone
B. Initiate high dose dexamethasone
C. Measure plasma free cortisol and/or salivary cortisol
D. Obtain pituitary MRI