Recognition of Adrenal Insufficiency – a Silent but Deadly Problem

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• Introduction
• Differential diagnosis
  – Primary Adrenal Insufficiency
  – Secondary Adrenal Insufficiency
• Clinical Manifestations
• Laboratory Evaluation
  – Corticotropin stimulation test
• Treatment
  – Replacement
  – Emergency
• Corticosteroids in septic shock

Normal Physiology

• About 90% of adrenal gland tissue consists of the adrenal cortex
  – Glomerulosa (aldosterone)
  – Fasciculata (cortisol)
  – Reticularis (adrenal androgens)
• Actions of cortisol
  – Counterregulatory hormone
  – Anti-inflammatory
  – Immunomodulation: dampens defense mechanisms, preventing dangerous overactivity
  – Inhibit NO; enhance catecholamine responses
  – Negative feedback on CRH, ACTH

• Cortisol is a vital hormone involved in carbohydrate and protein metabolism: stimulates the catabolism of peripheral fat and protein to provide substrates for gluconeogenesis.
  – 90% of cortisol is bound to CBG.
  – CBG is elevated 2-3 fold by estrogens.
• ACTH is synthesized as a large precursor, pro-opiomelanocortin (POMC), which is processed to ACTH, MSH, β-lipotropin, and β-endorphin which are secreted together.
• ACTH also stimulates secretion of adrenal androgens and, transiently, of aldosterone (mainly regulated by angiotensin II and [K]).

Adrenal Insufficiency

• Primary (Addison’s disease): Destruction of the adrenal cortex itself, resulting in deficiency of cortisol and aldosterone. Need over 90% destruction before symptoms occur.
• Secondary adrenal insufficiency: Pituitary or hypothalamic disease (usually see involvement of other hormonal axes, diabetes insipidus, ± neurologic, ophthalmologic manifestations if mass effect). Aldosterone deficiency is not a problem.

Causes of Addison’s Disease

• Adrenal destruction
• Adrenal dysgenesis/hypoplasia
• Impaired steroidogenesis
• Accelerated cortisol metabolism
  • Thyrotoxicosis
  • Drugs
Adrenal Destruction

• Autoimmune adrenalitis: The most common cause of Addison’s disease (~70% of cases), caused by slow destruction of the cortex by lymphocytes. Autoimmune adrenalitis usually spares the medulla.
  – May occur in isolation, or as part of multiple autoimmune endocrinopathy, often divided into APS-I, II (considerable overlap).

• Autoimmune hepatitis, s/p liver transplant x 2
• Hypoparathyroidism
• Addison’s dz, ACTH 457, Cortisol 12, 21OH ab 1.5 (nl 0-0.9)
• Candidiasis, esophageal, oral, onychal nails
• Alopecia totalis, transiently recovered hair after liver tx
• Testicular failure, LH 83, FSH 37, free T 42 (50-210), Total T 289
• Malabsorption, carotene < 2, 25-OH-D 12 (15-57), vitamin A 0.2 (0.3-0.9)
• TSH 4.4, TPO 2.4 (nl < 2)
• Type 1 DM, brittle, undetectable C peptide, GAD ab positive
• Autoimmune thyroid dz
• Addison’s dz
• Vitiligo
• Thrombocytopenia, s/p splenectomy, IVIG, CSA, phasmapheresis, vincristine

• Autoimmune polyglandular syndrome, type I (APECED): autosomal recessive, develops in childhood, dx requires 2 of following: adrenal insufficiency, hypoparathyroidism, mucocutaneous candidiasis. Also see hypogonadism, T1DM, chronic active hepatitis, alopecia universalis, vitiligo, malabsorption syndromes, juvenile-onset pernicious anemia. Mutation of the AIRE gene (thymus).
• APS-II (Schmidt/Carpenter syndrome, more common): adrenal insufficiency, thyroiditis, T1DM; onset in adulthood. May also see hypogonadism, celiac disease, vitiligo, pernicious anemia, alopecia, stiff-man syndrome, and serositis. Polygenic inheritance. Autoantigen: 21-hydroxylase (role in pathogenesis uncertain).

• Adrenoleukodystrophy: X-linked (thus, affects more men) peroxisomal disorder resulting in excess of very-long-chain (> 23 C) fatty acids. See adrenal insufficiency and CNS demyelination. Diagnosis by measuring hexacosanoic acid, MRI. Manage with diet change (restrict saturated fats). Also 4:1 glycerol trioleate:glycerol trierucate; BMT. Mutation in ABCD1 gene. 4 phenotypes:
  – Asymptomatic (15%)
  – Isolated adrenal insufficiency (15%)
  – Cerebral adrenoleukodystrophy (40%); onset age 5-12 of adrenal insufficiency and central demyelination leading to seizures, cortical blindness, dementia, coma, death, usually before puberty.
  – Adrenomyeloneuropathy (30%); age 15-30; spinal cord & peripheral neuronal involvement slowly progressing over 5-15 years; develop mixed motor & sensory peripheral neuropathy, bladder dysfunction, adrenal insufficiency, hypogonadism, color blindness. 1/3 develop central demyelination.

• Tuberculosis (10-15% of Addison’s dz). If suspected, must give antiTB meds. Giving corticosteroids alone can encourage TB spread.
• Metastatic disease (lung, kidney, colon, breast, esophagus, pancreas, liver, stomach, melanoma); lymphoma
• Infiltration: amyloidosis, hemochromatosis, syphilitic gumma, sarcoidosis, histiocytosis, Wolman disease
• Systemic fungal infections (histoplasmosis, cryptococcosis, coecidiomycosis, blastomycosis; not candida)
Symmetric demyelination in parieto-occipital region

- AIDS-associated: More than 50% of AIDS patients have pathologic evidence of necrotizing adrenalitis, but usually < 50% adrenal destruction. Clinical adrenal insufficiency occurs in <5% of patients with AIDS.
  - Opportunistic infection: CMV infection (accounts for >50% of cases of adrenal insufficiency in AIDS), MAI, MTB, fungi, Toxoplasma, Pneumocystis.
  - Kaposi's sarcoma, lymphoma.
  - Medications: ketoconazole (inhibits adrenal steroidogenesis); rifampin, phenytoin, opiates (increased steroid catabolism)
  - Secondary: Cytokines (IL-1, TNFα, IFN) released by macrophages in patients with AIDS may inhibit the hypothalamic-pituitary-adrenal (HPA) axis. CNS lymphoma, toxoplasmosis, basilar meningitis.

- Adrenal hemorrhage, thrombosis, infarction: seen mostly in gravely ill patients, possible etiologies:
  - Stress ACTH mediated increase in adrenal blood flow exceeding venous drainage → thrombosis → hemorrhage
  - Meningococcal or other kinds of sepsis (Pseudomonas, Staphylococcus aureus): Waterhouse-Friderichsen syndrome
  - Coagulation disorders or warfarin therapy
  - Antiphospholipid syndrome
  - Trauma: external trauma or invasive procedure (e.g. bilateral venography)

Adrenal dysgenesis/hypoplasia

- Congenital adrenal hypoplasia (DAX-1)
- Mutation of SF-1
- ACTH resistance syndromes
  - Familial glucocorticoid deficiency
    - FGD Type-1: mutation of ACTH receptor. Associated with tall stature, advanced bone age.
    - FGD Type-2: mutation in melanocortin-2 receptor accessory protein (MRAP).
  - Triple A (Allgrove’s syndrome): adrenal insufficiency, achalasia, alacrima
### Impaired Steroidogenesis
- Congenital adrenal hyperplasia (severe)
- Mitochondrial disorders
  - Kearns-Sayre syndrome
- Defective cholesterol metabolism
  - Smith-Lemli-Opitz syndrome
- Sitosterolemia
- Drug induced

### Drug-induced Adrenal Insufficiency
- Accelerated cortisol metabolism
  - Phenytoin, barbiturates, rifampin (CYP3A4 inducers)
- Mitotane (also toxic to adrenal tissue)
- Opioids
- Impaired steroidogenesis
  - Ketoconazole
  - Etomidate, including single injection for intubation
  - Aminoglutethimide, metyrapone, suramin
- Most risk to patients with limited pituitary or adrenal reserve.

### Secondary Adrenal Insufficiency
- Pituitary or metastatic tumor; craniopharyngioma; hypothalamic tumors
- Pituitary surgery or irradiation
- Head trauma, lesions of the pituitary stalk
- Lymphocytic hypophysitis
- Sarcoidosis; histiocytosis X; amyloidosis
- Empty sella syndrome
- Infectious: TB, fungi, Nocardia, actinomycosis
- Meds: megestrol, progesterone (high doses), valproate, intrathecal opioids

### Functional/Relative Adrenal Insufficiency
- During sepsis (not non-septic critical illness?), functional adrenal insufficiency (absence of a structural defect of the HPA axis) may occur
- High levels of inflammatory cytokines (IL-6, TNFα) inhibiting cortisol synthesis and/or inducing systemic or tissue-specific corticosteroid resistance.
  - ? Sepsis → iNOS → hypothalamic apoptosis
- Manifested by low cortisol response to ACTH, seen in 40-60% of patients with septic shock
- Controversial

### Clinical Manifestations
- Have a low index of suspicion; patients often have non-specific symptoms.
- Acute adrenal insufficiency can be lethal, suspect in setting of unexplained pressor-resistant hypotension, abdominal pain, vomiting, high fever, confusion (note: hyponatremia and hyperkalemia not always present).
- Up to 40% of Addison’s patients are normokalemic
Clinical Manifestations

Primary and secondary adrenal insufficiency
• Tiredness, weakness, mental depression
• Anorexia, weight loss
• Diarrhea, obstetric hyperemesis
• Abdominal cramps, N/V, diarrhea
• Hypertension, hypoglycemia
• Mild normocytic anemia, lymphopenia
• Hypercalcemia (rare)
• Loss of body hair in women
• Pale skin without marked anemia
• Amenorrhea, decreased libido and potency
• Scanty axillary and pubic hair
• Small testicles
• Secondary hypothyroidism
• Prepubertal growth defect, delayed puberty
• Headache, seizures
• Diabetes insipidus
• Hyperpigmentation*
• Hyperkalemia
• Vitiligo
• Autoimmune thyroid disease
• CNS symptoms in adrenomyeloneuropathy
• Salt craving
• Acidosis (Type IV RTA)

Secondary adrenal insuff. and associated disorder
• Pale skin without marked anemia
• Amenorrhea, decreased libido and potency
• Scanty axillary and pubic hair
• Small testicles
• Secondary hypothyroidism
• Prepubertal growth defect, delayed puberty
• Headache, seizures
• Diabetes insipidus

Laboratory Evaluation of Adrenal Function

• Cortisol measurement. Drawn before 9 a.m., a value ≤ 3 µg/dl indicates adrenal insufficiency, and concentrations ≥ 19 µg/dl rule it out. Intermediate values necessitate dynamic testing.
• Estrogen raises corticosteroid binding globulin concentrations, raising [cortisol].
• Normal range of cortisol is 6-24 µg/dl, in an ICU patient it should be ≥ 25 µg/dl. Consider ICU patient adrenally insufficient if < 15 µg/dl.
• ACTH measurement: helpful in primary adrenal insufficiency where [ACTH] > 100 pg/ml, even if the plasma cortisol is in the normal range. Normal ACTH values rule out primary but not mild secondary adrenal insufficiency.
• Aldosterone measurement (pre and post 250 µg cosyntropin): In primary insufficiency, will be low at baseline and not change (or blunted) after stimulation test; in secondary, baseline will be low or normal, and should increase in response to cosyntropin (by ≥ 4 ng/dl or 2X over baseline).
• Affected by volume, posture, potassium status.

*Due to MSH secreted with ACTH, noted usually around the lips, buccal membranes, posterior neck, nail beds and in exposed or pressure areas (eg. knuckles, elbows, belt line). New scars are pigmented. To find pigment changes in dark-skinned patients, look at palate and palmar creases.
Cosyntropin Test

- Short corticotropin stimulation test: 250 µg of cosyntropin (Cortrosyn) is given IV (rapid injection) or IM before 10 am (actually, can do test at any time of the day), and plasma cortisol measured 30-60 minutes later.
  - Some patients may fail at 30 minutes but pass at 60
  - Adrenal insufficiency ruled out if basal or post-stimulation cortisol is $\geq 18-20$ µg/dL (using higher cutoff minimizes underdiagnosis).

Cosyntropin Test

- This test picks up both primary and secondary (adrenal cortex atrophied) insufficiency.
- However, in secondary insufficiency, especially recent onset or mild, the test may be normal because 250 µg is highly supraphysiologic.
- Relative adrenal insufficiency
  - Basal cortisol 15-34 µg/dL
  - Failure to increase $> 9$ µg/dL after ACTH

Low Dose Cosyntropin Test

- Low-dose corticotropin test: 1 µg used instead of 250 µg. Test used to detect mild secondary adrenal insufficiency (eg. patient on inhaled glucocorticoids).
- Sampling at 20, 30 minutes.
- Normal response is cortisol $\geq 18$ µg/dl.

Other Tests

- Insulin-induced hypoglycemia, a test for secondary adrenal insufficiency since hypoglycemia stimulates the entire HPA axis. Use 0.1-0.15 U/kg insulin to obtain symptomatic (sympathetic activation) hypoglycemia (<40 mg/dl). Glucose, cortisol, ± ACTH are measured before and 15, 30, 45, 60, 75, and 90 minutes after insulin injection. Normal cortisol rises to 18-20 µg/dl.
- Corticotropin-releasing hormone stimulation test may also be used and can be helpful in distinguishing ACTH deficiency from CRH deficiency.
- 24-hr urine free cortisol is not used because it is normal in 20% of patients with adrenal insufficiency.
- Assays for adrenal autoantibodies (ACA, 21OH) are available, but their use is complicated by issues of assay sensitivity and transient seropositivity (diminish with time). However, a high screening titer (>1:16) of adrenal autoantibodies signifies high risk for adrenal failure (6-19% per year) and calls for functional monitoring. Dual positivity or high titers most diagnostic for autoimmune adrenalitis.
  - 21-hydroxylase antibody more sensitive than ACA

Replacement Therapy

- Goal is to find the lowest dose which relieves the patient’s symptoms, to prevent weight gain, osteoporosis, and cataracts. Replacement glucocorticoid is given in morning & afternoon.
- Classic dosage: 30 mg of hydrocortisone (20 mg, 10 mg) or 37.5 mg cortisone (25 mg, 12.5 mg) or 7.5 mg prednisone (5 mg, 2.5 mg; or once).
  - Newer: hydrocortisone 10 mg, 5 mg
  - TID dosing: weight-based dosing vs fixed
  - Food before HC dose delays its absorption
- In development: delayed release forms to better approximate diurnal variation

Limitations of Oral HC Dosing

Hydrocortisone: 10 mg at 6 am; 5 mg at noon; 2.5 mg at 6 pm
Four doses vs. two doses

Four-dose regimen associated with higher 7 am cortisol and lower 7 am ACTH, higher 24-hr cortisol and lower 24-hr ACTH (AUC) and was preferred by patients.

10 mg
12 pm: 10 mg
4 pm: 5 mg
10 pm: 5 mg

7 am: 20 mg
4 pm: 10 mg

Ekman B. et al. Clin Endocrinol 2012 Epub Jan 12

Three times daily, weight-based hydrocortisone dosing

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Total daily dose (mg)</th>
<th>1st morning dose</th>
<th>2nd midday dose</th>
<th>3rd evening dose</th>
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<tbody>
<tr>
<td>50-54</td>
<td>10</td>
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<td>115-120</td>
<td>25</td>
<td>15</td>
<td>7.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Debono M, Ross RJ. Clin Endocrinol 2013;78:659-664

Replacement Therapy

- If primary adrenal insufficiency, give fludrocortisone (Florinef), in a single daily dose, 0.05-0.2 mg (usually 0.1 mg/d), with adjustments per BP, serum potassium, peripheral edema, and plasma renin activity (upper-normal range).
- Patients should carry a card or med-alert bracelet, and should be advised to double or triple the dose of hydrocortisone temporarily when they have any febrile illness or injury, and should be given ampules of glucocorticoid for injection or suppositories to be used if they are vomiting.

Emergency Therapy

- Immediate high dose IV hydrocortisone 100 mg bolus, followed by an infusion of 100-200 mg over the next 24 hours or intermittent IV dosing at 50-100 mg q 6-8 hours. This is enough to give mineralocorticoid action, so do not need florinef until taper down to oral glucocorticoids (or once hydrocortisone is < 100 mg/day).
- Hypovolemia and hyponatremia: IV normal saline, volume needed may be large and should be supplemented by glucose.

What is “Stress Dose”??

- Tailor to the clinical picture
- Range for hydrocortisone:
  - 20 mg/10 mg PO to 100 mg IV q6 hrs
  - Everything in between can be used
    - 50 mg q12 hr
    - 50 mg q8 hr
    - 100 mg q8 hr
    - etc.

Corticosteroids in Shock

- Early trials: high doses for short duration (> 300 mg/d HC, for < 5 days): no mortality benefit
- Later trials (vasopressor-dependent shock): lower doses, longer duration (200-300 mg/d, 5-11 days): accelerated shock reversal, improved survival at 28 days, improved ICU mortality
- Treat all patients versus only those with diagnosed relative adrenal insufficiency?
- What are we treating? Severe inflammation vs adrenal insufficiency

Relative Adrenal Insufficiency

- Shock patients with cortisol increment < 9 µg/dL had increased mortality in some but not all studies
- Higher baseline cortisol → lower increment
- Severe stress: baseline cortisol similar to ACTH-stimulated cortisol in non-stressed
  - ACTH can further increase cortisol in stressed patients:
    - clinical significance if already maximally stimulated
- Benefit of corticosteroids in shock may have nothing to do with adrenal insufficiency

Major Clinical Trials in Septic Shock

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrollment window (time since shock onset)</th>
<th>Daily dose</th>
<th>Duration</th>
<th>% patients non-responsive to ACTH</th>
<th>Death rate in placebo group</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane JAMA 2002 N=300</td>
<td>8 hours, vasopressor unresponsive</td>
<td>HC 200 mg, fludrocortisone 50 mcg</td>
<td>7 days</td>
<td>77%</td>
<td>61% (sicker patients)</td>
<td>In ACTH non-responders only: reduced death &amp; duration of vasopressors</td>
</tr>
<tr>
<td>CORTICUS NEJM 2008 N=500 (planned=800)</td>
<td>72 hours, could be vasopressor responsive</td>
<td>HC 200 mg, then taper</td>
<td>5 days, then tapered over 6 days</td>
<td>47%</td>
<td>32%</td>
<td>No mortality difference, regardless of ACTH response. Time to shock reversal shortened. Higher superinfection, new shock, hyperglycaemia, hypernatremia.</td>
</tr>
</tbody>
</table>

Clinical Trials in Septic Shock

- In most patients, ACTH testing to search for relative adrenal insufficiency might provide prognostic information, but hydrocortisone treatment does not reduce mortality
- There might be a role in patients with severe, vasopressor-resistant septic shock who are diagnosed and treated early (<8 hr)