Adrenal Insufficiency: Current Practice 2012

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Overview

- A very brief review of adrenal function
- What is adrenal insufficiency?
- Adrenal insufficiency in the outpatient setting
- Adrenal insufficiency during critical illness
- Therapy for adrenal insufficiency
• Actions of Aldosterone
  – Promotes sodium/water retention
  – Promotes potassium excretion
  – May be involved in tissue remodeling (e.g. in the heart)

• Actions of adrenal androgens
  – Responsible for initiation of puberty
    • Secondary sex characteristics in women

What is Adrenal insufficiency?

• When discussing adrenal insufficiency (Addison disease), we are almost always talking about glucocorticoid (cortisol) insufficiency

• However, other adrenal hormones can also be affected in primary adrenal failure

Adrenal Insufficiency (Addison disease)

Clinical Addison disease

Image courtesy of Wellcome Images
http://images.wellcome.ac.uk/
Clinical Features of Chronic Adrenocortical Insufficiency

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

»more common in children and women

Features of Acute Adrenocortical Insufficiency (Adrenal Crisis)

- Hypotension
- Weakness (prox. muscle), confusion
- Nausea, vomiting, abdominal pain
- Dehydration, hypovolemia
- Hyperthermia
- Hypoglycemia

TREAT FIRST, AND DIAGNOSE LATER!!

Addison disease

Hyperpigmentation, toxic appearance

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)
Normal Adrenal Function

[Diagram showing the normal adrenal function pathway involving the hypothalamus, pituitary, and adrenals, with cortisol and aldosterone.]  

Secondary Adrenal Insufficiency

[Diagram showing the secondary adrenal insufficiency pathway involving the hypothalamus, pituitary, and adrenals, with cortisol and aldosterone.]  

Primary Adrenal Insufficiency

[Diagram showing the primary adrenal insufficiency pathway involving the hypothalamus, pituitary, and adrenals, with cortisol and aldosterone.]  

Causes of adrenal failure

- Like CS, iatrogenic causes are probably most common
- Inherited forms of adrenal failure
  - Typically presenting early in life (<1 yr)
    - CAH, especially salt-wasters (steroid biosynthesis defect)
    - Other rare genetic diseases (lipoid CAH, AHC)
  - Typically presenting in childhood, and dx should be "obvious"
    - AAA
      - Alacrima, Achalasia, Adrenal failure
    - Autoimmune Polyendocrine Syndrome (APS), Type I (APECED)
      - Ectodermal dysplasia, mucocutaneous candidiasis

- Primary
  - Adrenal gland
  - Destruction of glands

- Secondary
  - Pituitary
  - Inadequate ACTH
  - NO increased pigment
  - Fewer electrolyte imbalances

(regulated by Renin/Angiotension system)
**Causes of adrenal failure**

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- Presenting later in life
  - Autoimmune Polyendocrine Syndrome (APS), Type II
    - Type I DM, thyroid disease
    - May occur as sole autoimmune feature (although rare)
  - Adrenal hemorrhage
    - Resulting from sepsis
    - HIV, other viral diseases
    - Adrenalectomy
  - Note that non-classical CAH rarely causes adrenal insufficiency
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
    - Metastatic disease

Diagnosis of Adrenal Insufficiency in the Outpatient setting: Static Testing

- A GOOD HISTORY IS ESSENTIAL!
  - History of steroid use, including nasal steroids or injected steroids (e.g., back injections)

- 8 AM cortisol (probably NOT reliable in hospitalized patients)
Diagnosis of Adrenal Insufficiency in the Outpatient setting: Static Testing

- ACTH measurements
  - Generally not helpful, particularly low values
  - Elevated values may suggest primary Adrenal Insufficiency in the right clinical setting

- “Suggestive” findings:
  - Eosinophilia, hyperchloremia, acidosis, hypercalcemia, azotemia, hyponatremia/hyperkalemia and fasting hypoglycemia

Adrenal Insufficiency: ACTH stim test

- Give IV/IM bolus of 250 mcg ACTH, measure blood at 0, 30, 60 min
- Normal response is for cortisol to reach >18 mcg/dl
- Caveat: ACTH stim test will be “normal” in early pituitary failure. Once adrenal atrophy sets in, test becomes subnormal

Adrenal Insufficiency during Critical Illness

- Adrenal function during critical illness
- Relative adrenal insufficiency
- Overview of Corticosteroid therapy in the ICU
- Conclusions
Adrenal Function in Critical Illness

- **Adrenal Gland**
  - Synthetic inhibition
    - Drugs
      - Etomidate
      - Ketoconazole
    - Cytokines
  - Destruction
    - Pre-existing
      - Autoimmune
      - Infection
        - HIV
        - CMV
        - TB
        - Fungal
        - Metastasis
    - Acute
      - Hemorrhage
      - Infection

The Adrenal Response to Prolonged Critical Illness

- ↑ Hepatic metabolism of cortisol
  - Rifampin
  - Phenytoin
  - Phenobarbital
- Glucocorticoid Resistance

“The fact that cortical hormone therapy exerts beneficial effects in so many conditions makes it rather likely that the hormone is not a specific antidote in any one of these cases but raises shock resistance in general because a condition of relative adrenal insufficiency exists in organisms exposed to non-specific damage.”

Cortisol Levels - Marker of Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal cortisol</th>
<th>Δ max</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>30%</td>
<td>&lt;34</td>
<td>&gt;9</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1%</td>
<td>&lt;34</td>
<td>&lt;9</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;34</td>
<td>&gt;9</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>20%</td>
<td>&gt;34</td>
<td>&lt;9</td>
</tr>
</tbody>
</table>

Annane JAMA 2000; 283:1038-1045
Steroids In Septic Shock

Catecholamine dependent septic shock (300)

Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

[Chart for the Catecholamine Test]


Effect of Low Dose Hydrocortisone on Mortality in Patients with Septic Shock

[Graph showing mortality rates]

Steroids In Septic Shock

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Non-Responders</th>
<th>Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>28 Day</td>
<td>53%*</td>
<td>63%</td>
</tr>
<tr>
<td>ICU</td>
<td>58%*</td>
<td>70%</td>
</tr>
<tr>
<td>Hospital</td>
<td>61%*</td>
<td>72%</td>
</tr>
<tr>
<td>1 Year</td>
<td>68%*</td>
<td>77%</td>
</tr>
</tbody>
</table>

Vasopressor Withdrawal

| (28 days) | Median | 40% | 50% | 53% |

Annane JAMA 2002; 288:862-871

Approach to Suspected Adrenal Insufficiency

- < 25 ug/dL
- 25 ug/dL to 40 ug/dL
- > 40 ug/dL

ACTH stim test

- < 9 ug/dL
- > 9 ug/dL

Persistent hypotension

Therapeutic Trial

Steroid Replacement Treatment

Effects of Corticosteroids on Mortality ICU Severe Sepsis and Septic Shock

<table>
<thead>
<tr>
<th>All trials</th>
<th>Treatment</th>
<th>Control</th>
<th>Relative risk (95%)</th>
<th>Weight</th>
<th>Relative risk (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All trials</td>
<td>All trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Billet 1998</td>
<td>6/22</td>
<td>15/19</td>
<td>0.90 (0.60 to 1.31)</td>
<td>9.66</td>
<td>0.60 (0.40 to 0.90)</td>
</tr>
<tr>
<td>Brogel 1999</td>
<td>4/20</td>
<td>8/20</td>
<td>1.00 (0.51 to 1.94)</td>
<td>4.45</td>
<td>0.97 (0.42 to 2.19)</td>
</tr>
<tr>
<td>Chatas 1998</td>
<td>6/23</td>
<td>6/21</td>
<td>1.00 (0.51 to 1.94)</td>
<td>6.49</td>
<td>0.88 (0.54 to 1.43)</td>
</tr>
<tr>
<td>Annane 2002</td>
<td>95/151</td>
<td>101/140</td>
<td>1.00 (0.74 to 1.34)</td>
<td>79.87</td>
<td>0.88 (0.74 to 1.06)</td>
</tr>
<tr>
<td>Total (95%) CI</td>
<td>216</td>
<td>280</td>
<td>100.0</td>
<td>0.83 (0.70 to 0.97)</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: τ²=20.8, I²=74.4%
Test for overall effect: z=3.26, P=0.001

Annane BMJ 2004:329:480

Concerns

- High mortality in the Control group
- Use of Etomidate
- Design and power
- Severe refractory shock required for enrollment
Hydrocortisone Therapy for Patients with Septic Shock
Sprung et al NEJM 2008

Enrolment and Outcome
Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults

JAMA 2010;303:341-348

Corticosteroids for ARDS NEJM 2006 “ARDSNET”

Figure 2. Probability of Survival and the Proportion of Patients with Persistent ARDS Who Became Able to Breathe without Assistance during the First 48 Days after Randomization.

Days after Randomization

Role of Steroids in Specific Conditions

<table>
<thead>
<tr>
<th>Good</th>
<th>Bad</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Meningitis</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>Pneumocystis Carinii Pneumonia</td>
<td>Sepsis?</td>
</tr>
<tr>
<td>No evidence</td>
<td>Fibroproliferative ARDS?</td>
</tr>
</tbody>
</table>
Surviving Sepsis 2008

- We suggest that intravenous hydrocortisone be given only to adult septic shock patients after it has been confirmed that their blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy (grade 2C).
- We suggest that the ACTH stimulation test not be used to identify the subset of adults with septic shock who should receive hydrocortisone (grade 2B).
- We suggest that patients with septic shock should not receive dexamethasone if hydrocortisone is available (grade 2B).

- daily addition of oral fludrocortisone (50 µg) if hydrocortisone is not available and the steroid that is substituted has no significant mineralocorticoid activity. Fludrocortisone is considered optional if hydrocortisone is used (grade 2C).
- that clinicians wean the patient from steroid therapy when vasopressors are no longer required (grade 2D).
- We recommend that doses of corticosteroids comparable to >300 mg hydrocortisone daily not be used in severe sepsis or septic shock for the purpose of treating septic shock (grade 1A).
- that corticosteroids not be administered for the treatment of sepsis in the absence of shock. (grade 1D).

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Treatment of Adrenal Insufficiency
**Treatment of Adrenal Insufficiency: Glucocorticoid Replacement**

<table>
<thead>
<tr>
<th>Glucocorticoid equivalents</th>
<th>Treatment of Adrenal Insufficiency: Mineralocorticoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hydrocortisone</td>
<td>• Replacement of mineralocorticoid needed if primary adrenal failure</td>
</tr>
<tr>
<td>– Metabolized to cortisol</td>
<td>• Florinef is synthetic mineralocorticoid (fludrocortisone)</td>
</tr>
<tr>
<td>– Approx 10-12 mg/m² is replacement dose of HC</td>
<td>– Comes in only 1 size (100 mcg)</td>
</tr>
<tr>
<td>– In most people, this is about 20-25 mg/day</td>
<td>– Most patients need 1 tab/day, but may need to titrate to symptoms or electrolytes</td>
</tr>
<tr>
<td>• 5’9”, 155 lb patient. BSA = 1.85. Dose = 18-22 mg</td>
<td>– In patients on high dose HC (&gt;50 mg/day), enough MC activity so that florinef not usually needed</td>
</tr>
<tr>
<td>• 6’, 300 lb patient. BSA = 2.63. Dose = 26-31 mg</td>
<td>– Mimic the diurnal variation (2/3 steroid AM; 1/3 evening)</td>
</tr>
<tr>
<td>– Evening dose given mid afternoon (e.g., 3pm) unless patient is night owl</td>
<td>– Can also be given as single AM dose if patient tolerates</td>
</tr>
<tr>
<td>– Can also be given as single AM dose if patient tolerates</td>
<td>– Synthetic steroids have longer half life, and may have increased incidence of side effects (e.g., osteoporosis, weight gain, immune suppression)</td>
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**Glucocorticoid equivalents**

<table>
<thead>
<tr>
<th>Hydrocortisone: 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone acetate: 25 mg</td>
</tr>
<tr>
<td>Prednisone 4-5 mg</td>
</tr>
<tr>
<td>Prednisolone 5 mg</td>
</tr>
<tr>
<td>Dexamethasone 0.75-1 mg</td>
</tr>
</tbody>
</table>
  – Synthetic steroids have longer half life, and may have increased incidence of side effects (e.g., osteoporosis, weight gain, immune suppression) |

**Treatment of Adrenal Insufficiency: Androgens**

| Anecdotal evidence suggests that replacing DHEA(S) may help improve patient well-being, but randomized studies have all been NEGATIVE |
| Patients may benefit from a trial of DHEA 50 mg. |
  – Patient feels better → great! |
  – No better → stop. |
### Treatment of Adrenal Insufficiency: Efficacy

- There is no single lab test that will judge adequacy of replacement, so patient symptomatology important
- **ACTH goals:**
  - Generally, aim for AM ACTH 50-150 pg/ml [normal 10-50]
  - Lower ACTH values generally indicate overtreatment
- **Renin goals:**
  - Normalized
  - Note that it may be very difficult to control ACTH levels if patient has significant mineralocorticoid deficient

### Recovery from critical illness

- Patients that are suspected of having adrenal insufficiency should have their steroids weaned once critical illness has resolved
- Typically, patients can be weaned to replacement level treatment at the time of discharge
- Further evaluation and tapering can then be done in the outpatient setting

### Recovery from Addison’s?

- Patients who fail an ACTH stim should be retested to verify
- Patients with Cushing Syndrome that are cured by surgery will be insufficient until their axis recovers
  - Requirement for steroids post-op is a **good** sign
  - Patients with Cushing syndrome can take 1-2 years to recover
- Patients on chronic steroids for many years may take **many years** to recover their axis

### Facilitating HPA recovery

- **Use Hydrocortisone**
  - Shorter biological half-life means axis can recover while patient on therapy
  - If patient tolerates, put on once daily replacement of HC and wait
    - Go for lowest dose that patient will tolerate
  - Retest by ACTH stim q3-4 months until recovery
- Can also use prednisone (low dose or qod dosing) but usually doesn’t work as well