Adrenal Insufficiency: Adrenal Insufficiency: Current Practice 2012

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Division of Endocrinology, Diabetes, and Metabolism
The Ohio State University’s Wexner Medical Center

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
Hypothalamus-Pituitary-Adrenal Axis

Stress (physical, psychological)

CRH or Vasopressin

ACTH: Major direct regulator of cortisol secretion

Adrenals

Cortisol, Aldosterone, Androgens

Actions of cortisol
• 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

Adrenal Insufficiency (Addison disease)

Image courtesy of Wellcome Images
http://images.wellcome.ac.uk/
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.

Clinical Addison disease
### Clinical Features of Chronic Adrenocortical Insufficiency

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness, fatigue</td>
<td>100%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>100%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>100%</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>92%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>88%</td>
</tr>
<tr>
<td>Nausea, abdominal pain</td>
<td>56%</td>
</tr>
<tr>
<td>Salt craving</td>
<td>19%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>??</td>
</tr>
</tbody>
</table>

»more common in children and women

---

**Addison disease**

Hyperpigmentation, toxic appearance

Hyperpigmentation, including knuckles and palmar creases

Images courtesy of Wellcome Images

http://images.wellcome.ac.uk/
<table>
<thead>
<tr>
<th>Features of Acute Adrenocortical Insufficiency (Adrenal Crisis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypotension</td>
</tr>
<tr>
<td>• Weakness (prox. muscle), confusion</td>
</tr>
<tr>
<td>• Nausea, vomiting, abdominal pain</td>
</tr>
<tr>
<td>• Dehydration, hypovolemia</td>
</tr>
<tr>
<td>• Hyperthermia</td>
</tr>
<tr>
<td>• Hypoglycemia</td>
</tr>
</tbody>
</table>

TREAT FIRST, AND DIAGNOSE LATER!!

---

<table>
<thead>
<tr>
<th>Adrenal Crisis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute loss of adrenal function</td>
</tr>
<tr>
<td>– Acute loss of adrenals</td>
</tr>
<tr>
<td>• Surgery</td>
</tr>
<tr>
<td>• Hemorrhage/thrombosis</td>
</tr>
<tr>
<td>– Acute loss of pituitary function</td>
</tr>
<tr>
<td>– Acute loss of steroid replacement</td>
</tr>
</tbody>
</table>
| OR
| • Acute stress in the setting of compensated chronic adrenal failure |
|   – Precipitating event (e.g., like DKA)                      |
Normal Adrenal Function

Hypothalamus → ↑ CRH → Pituitary → ↓ ACTH → Adrenals → ↓ Cortisol, Aldosterone

Primary Adrenal Insufficiency

• Primary
  – Adrenal gland
  – Destruction of glands

Hypothalamus → ↑ CRH → Pituitary → Adrenals → × Cortisol, Aldosterone
Secondary Adrenal Insufficiency

- **Primary**
  - Adrenal gland
  - Destruction of glands

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

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
### Causes of adrenal failure

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      - Ectodermal dysplasia, mucocutaneous candidiasis

- 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)**

<table>
<thead>
<tr>
<th>8am Cortisol (ug/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>25</td>
</tr>
</tbody>
</table>

- **Normal range**
- **Strongly suggestive**
- **Very unlikely**
### Diagnosis of Adrenal Insufficiency in the Outpatient setting: Static Testing - 2

- **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

### Diagnosis of 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

![Cortisol ug/dl graph]

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Cortisol ug/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>60</td>
<td>20</td>
</tr>
</tbody>
</table>
## Adrenal Insufficiency: Current Practice 2012

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Associate Professor  
Pulmonary, Critical Care, and Sleep Medicine  
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### Adrenal Insufficiency during Critical Illness

- Adrenal function during critical illness  
- Relative adrenal insufficiency  
- Overview of Corticosteroid therapy in the ICU  
- Conclusions
Acute injury

Death

Acute critical illness

Recovery

Sub-acute; chronic critical illness

Maladaptive responses

Adaptive responses

Impaired immune response

Adrenal function

Decreased inflammatory response

The Adrenal Response to Prolonged Critical Illness

### Adrenal Function in Critical Illness

<table>
<thead>
<tr>
<th>Adrenal Gland</th>
<th>Synthetic inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adrenal Gland</td>
<td>• Synthetic inhibition</td>
</tr>
<tr>
<td>• Drugs</td>
<td>• Cytokines</td>
</tr>
<tr>
<td>• Etomidate</td>
<td></td>
</tr>
<tr>
<td>• Ketoconazole</td>
<td>» Corticosteroids</td>
</tr>
<tr>
<td>• Destruction</td>
<td>• Acute</td>
</tr>
<tr>
<td>• Pre-existing</td>
<td>• Glucorticoid Resistance</td>
</tr>
<tr>
<td>• Autoimmune</td>
<td></td>
</tr>
<tr>
<td>• Infection</td>
<td></td>
</tr>
<tr>
<td>• HIV • CMV</td>
<td>• Hemorrhage</td>
</tr>
<tr>
<td>• TB • Fungal</td>
<td>• Infection</td>
</tr>
<tr>
<td>• Metastasis</td>
<td></td>
</tr>
</tbody>
</table>

### Adrenal Function in Critical Illness

| ↑ Hepatic metabolism of cortisol | |
| • Rifampin | |
| • Phenytoin | |
| • Phenobarbital | |
| • Glucorticoid 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

Venkatesh and Cohen 2011
Cortisol and Septic Shock

<table>
<thead>
<tr>
<th>% Basal cortisol</th>
<th>△ max</th>
<th>mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good 30% &lt; 34 &gt; 9</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Intermediate 1</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Intermediate 2</td>
<td>82%</td>
<td></td>
</tr>
</tbody>
</table>

Annane JAMA 2000; 283:1038-1045

Prognostic Value of Cortisol Levels and ACTH Response

Steroids In Septic Shock

Catechlamine dependent septic shock (300)

ACTH Stim Test

76% Non-Responders (229)

<9 ug/dl cortisol

Steroids

50 mg Hydrocortisone q6º

50 ug Fludrocortisone qd

Placebo

24% Responders (70)

>9 ug/dl cortisol

Steroids

50 mg Hydrocortisone q6º

50 ug Fludrocortisone qd

Placebo

Annane JAMA 2002; 288:862-871
Effect of Low Dose Hydrocortisone on Mortality in Patients with Septic Shock

Annane, D. et al. JAMA 2002;288:862-871
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>Steroids</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)

- 57%* median 7
- 40% median 10
- 50% median 9
- 53% median 7

Annane JAMA 2002; 288:862-871

Effects of Corticosteroids on Mortality

ICU     Severe Sepsis and Septic Shock

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Relative risk (fixed)</th>
<th>Weight (%)</th>
<th>Relative risk (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All trials</td>
<td></td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>Bollard 1998</td>
<td>8/22</td>
<td>12/19</td>
<td>9.99</td>
<td>0.58</td>
<td>(0.30 to 1.10)</td>
</tr>
<tr>
<td>Brigiel 1999</td>
<td>4/20</td>
<td>6/20</td>
<td>4.65</td>
<td>0.67</td>
<td>(0.22 to 2.01)</td>
</tr>
<tr>
<td>Chaulo 1999</td>
<td>5/23</td>
<td>8/21</td>
<td>6.49</td>
<td>0.68</td>
<td>(0.39 to 1.65)</td>
</tr>
<tr>
<td>Annane 2002</td>
<td>90/151</td>
<td>101/149</td>
<td>78.67</td>
<td>0.66</td>
<td>(0.74 to 1.94)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>216</td>
<td>208</td>
<td>100.0</td>
<td>0.83</td>
<td>(0.70 to 0.97)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: χ²=2.01, df=3, p=0.57, I²=0%  
Test for overall effect: χ²=2.28, p=0.13  
Favours treatment Favours control

Annane BMJ 2004;329:480
Approach to Suspected Adrenal Insufficiency

- **< 25 ug/dL**
  - ACTH stim test
  - < 9 ug/dL
  - Persistent hypotension
  - Steroid Replacement Treatment

- **25 ug/dL to 40 ug/dL**

- **> 40 ug/dL**
  - > 9 ug/dL
  - Therapeutic Trial

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
Hydrocortisone Therapy for Patients with Septic Shock
Kaplan–Meier curves for survival at 28 days according to response to corticotropin test

Sprung et al NEJM 2008
Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults

JAMA 2010;303:341-348

### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intensive Insulin Therapy (n = 254)</th>
<th>Conventional Glucose Control (n = 254)</th>
<th>P Value</th>
<th>Hydrocortisones + Glucose Control (n = 248)</th>
<th>P Value</th>
<th>Hydrocortisones + Glucose Control (n = 264)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital death</td>
<td>11.7 (6.9)</td>
<td>15.9 (12.3)</td>
<td>0.50</td>
<td>0.37</td>
<td>0.55 (4.8)</td>
<td>0.60</td>
<td>0.91</td>
</tr>
<tr>
<td>Deaths, No. (%)</td>
<td>122 (47.9)</td>
<td>118 (46.5)</td>
<td></td>
<td></td>
<td>112 (45.7)</td>
<td>128 (48.5)</td>
<td></td>
</tr>
<tr>
<td>Kaplan-Meier estimate of survival rates, 0.95 confidence interval, in 55% (95% CI)</td>
<td>1.92 (0.80-1.34)</td>
<td>1.94 (0.83-1.21)</td>
<td>0.75</td>
<td>0.79</td>
<td>0.75 (0.34-1.75)</td>
<td>0.61</td>
<td>0.67</td>
</tr>
<tr>
<td>28</td>
<td>62.5 (56.4-68.5)</td>
<td>61.1 (55.3-67.5)</td>
<td>62.5 (56.4-68.5)</td>
<td>60.9 (55.2-67.3)</td>
<td>60.9 (55.2-67.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>51.6 (45.0-59.4)</td>
<td>54.6 (48.9-61.4)</td>
<td>54.6 (48.9-61.4)</td>
<td>55.4 (49.6-69.2)</td>
<td>55.4 (49.6-69.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>50.0 (40.0-57.6)</td>
<td>52.1 (46.2-58.8)</td>
<td>52.1 (46.2-58.8)</td>
<td>50.2 (44.4-56.3)</td>
<td>50.2 (44.4-56.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. of patients who died 103 92 121

### Causes of Death

<table>
<thead>
<tr>
<th>Causes of death, No. (%)</th>
<th>Multisystem organ failure</th>
<th>Cardiovascular</th>
<th>Stroke</th>
<th>Brain hemorrhage</th>
<th>Refractory hypoxia</th>
<th>Unknown</th>
<th>Multisystem organ failure</th>
<th>Cardiovascular</th>
<th>Stroke</th>
<th>Brain hemorrhage</th>
<th>Refractory hypoxia</th>
<th>Unknown</th>
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<th>Brain hemorrhage</th>
<th>Refractory hypoxia</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive Insulin Therapy (n = 254)</td>
<td>90 (35.6)</td>
<td>93 (35.3)</td>
<td>11 (4.3)</td>
<td>20 (7.9)</td>
<td>10 (3.9)</td>
<td>3 (1.2)</td>
<td>75 (29.1)</td>
<td>73 (28.8)</td>
<td>3 (1.2)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional Glucose Control (n = 254)</td>
<td>66 (26.0)</td>
<td>76 (29.8)</td>
<td>17 (6.7)</td>
<td>25 (9.9)</td>
<td>14 (5.5)</td>
<td>2 (0.8)</td>
<td>83 (32.7)</td>
<td>79 (30.8)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisones + Glucose Control (n = 248)</td>
<td>0.004</td>
<td>0.005</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisones + Glucose Control (n = 264)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
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</tr>
</tbody>
</table>

### Mortality:

- **All patients**: 9 (4.19) 9 (4.19) 10 (4.19) 9 (4.19) 9 (4.19) 10 (4.19)
- **All patients with SCFA**: 16 (6.34) 15 (5.79) 8.7 (4.30) 14 (6.25) 18 (7.34) 15 (6.34)
- **Survivors**: 24 (12.43) 22 (11.98) 8.7 (5.7) 19 (6.43) 25 (14.28) 19 (6.34)

JAMA 2010;303:341-348
Corticosteroids for ARDS
NEJM 2006 “ARDSNET”

Role of Steroids in Specific Conditions

<table>
<thead>
<tr>
<th>Good</th>
<th>Bad</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Meningitis</td>
<td>Industrial strength pharmacologic does</td>
</tr>
<tr>
<td>• Typhoid fever</td>
<td></td>
</tr>
<tr>
<td>• Spinal cord injury</td>
<td></td>
</tr>
<tr>
<td>• Pneumocystis Carinii Pneumonia</td>
<td></td>
</tr>
<tr>
<td>• No evidence</td>
<td></td>
</tr>
<tr>
<td>▪ Fibroproliferative ARDS?</td>
<td></td>
</tr>
<tr>
<td>▪ Sepsis?</td>
<td></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).

Surviving Sepsis 2008

• 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

- Hydrocortisone
  - Metabolized to cortisol
  - Approx 10-12 mg/m2 is replacement dose of HC
  - In most people, this is about 20-25 mg/day
    - 5'9”, 155 lb patient. BSA = 1.85. Dose = 18-22 mg
    - 6', 300 lb patient. BSA = 2.63. Dose = 26-31 mg
  - 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
  - Can also be given as single AM dose if patient tolerates

Glucocorticoid equivalents

- Hydrocortisone: 20 mg
- Cortisone acetate: 25 mg
- Prednisone 4-5 mg
- Prednisolone 5 mg
- Dexamethasone 0.75-1 mg
  - Synthetic steroids have longer half life, and may have increased incidence of side effects (e.g., osteoporosis, weight gain, immune suppression)
<table>
<thead>
<tr>
<th>Treatment of Adrenal Insufficiency: Mineralocorticoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Replacement of mineralocorticoid needed if primary adrenal failure</td>
</tr>
<tr>
<td>• Florinef is synthetic mineralocorticoid (fludrocortisone)</td>
</tr>
<tr>
<td>– Comes in only 1 size (100 mcg)</td>
</tr>
<tr>
<td>– Most patients need 1 tab/day, but may need to titrate to symptoms or electrolytes</td>
</tr>
<tr>
<td>– In patients on high dose HC (&gt;50 mg/day), enough MC activity so that florinef not usually needed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment of Adrenal Insufficiency: Androgens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anecdotal evidence suggests that replacing DHEA(S) may help improve patient well-being, but randomized studies have all been NEGATIVE</td>
</tr>
<tr>
<td>• Patients may benefit from a trial of DHEA 50 mg.</td>
</tr>
<tr>
<td>– Patient feels better → great!</td>
</tr>
<tr>
<td>– No better → stop.</td>
</tr>
</tbody>
</table>
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 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
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

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