Assessing Adrenal Function in Ill, Hospitalized Patients

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Disclosures

- Very surprised when I received an email two weeks ago disclosing I was speaker today.

- No conflicts or financial interests.
Endocrine Diagnosis

Symptoms

Signs

Hormone assessment
Outline

- Normal physiology and response to stress.
- Evaluation of patients for adrenal insufficiency.
- Patients on exogenous glucocorticoids.
- Critically ill patients.
Hypothalamus

CRH

Pituitary

ACTH

Stress
- hypotension
- fever
- trauma/surgery
- hypoglycemia

Cortisol

Adrenal Cortex

Stress

CRH
Cortisol Levels in Acutely Ill Patients

![Graph showing cortisol levels in different conditions]

- GI bleed
- Acute MI
- Respiratory failure
- Sepsis
- Shock
# Glucocorticoid Physiology

<table>
<thead>
<tr>
<th></th>
<th>Excess</th>
<th>Deficiency</th>
</tr>
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<tbody>
<tr>
<td>Metabolic</td>
<td>Hyperglycemia, protein breakdown, lipolysis</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>HTN</td>
<td>Hypotension</td>
</tr>
<tr>
<td>GI</td>
<td>Incr appetite, wt gain</td>
<td>Anorexia, wt loss, N/V</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Muscle atrophy, bone loss</td>
<td>Weakness</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>Immune suppression</td>
<td>Anemia</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Depression, psychosis, mood change</td>
<td>Lethargy, apathy</td>
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</tbody>
</table>
24 Hr Cortisol Levels in Healthy People

**Figure 1.** Plasma cortisol values of normal subjects for 24-hr periods of study. Samples obtained every 20 min. Period of time of "lights out" is sleep period available.

Weitzman JCEM 1971
Cosyntropin Stimulation Test

Serum cortisol response to 0.25 mg of cosyntropin in normal subjects (n = 9), hypopituitarism (n = 8), and Addison’s disease (n = 7). P < .01 between all means except zero times in primary and secondary adrenal insufficiency.

Speckart Arch IM 1971
Cosyntropin – Low Dose or High Dose

Tordkman JCEM 1995
Patients on Exogenous Steroids
## Relative Potency

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Equivalent Dose (mg)</th>
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<tbody>
<tr>
<td>Hydrocortisone</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Prednisone</td>
<td>2.5 - 5</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.5 - 1</td>
</tr>
</tbody>
</table>
Recovery of the H-P-A Axis

Graber, JCE 1965.
Predicting Adrenal Suppression

THE EFFECT OF LONG-TERM GLUCOCORTICOID THERAPY ON PITUITARY–ADRENAL RESPONSES TO EXOGENOUS CORTICOTROPIN-RELEASING HORMONE

Reiner Schlaghecke, M.D., Ph.D., Elisabeth Kornely, M.D., Reinhard Th. Santen, M.D., and Paul Ridderskamp, M.D.
Cortisol Response to CRH – Patients on GC Therapy
Predicting Response

No correlation of cortisol response to dose, duration or cumulative dose of GC

~ 25% on < 10 mg prednisone had no response; ~ 25% on > 25 mg had normal response.

~ 25% with 1-8 weeks exposure had no response; 30% with > 100 weeks had normal response.

Predict response to CRH based on basal cortisol level only about 60% patients.
Exogenous GC at dose equivalent of prednisone 7.5 mg a day for 1 – 3 weeks may result in adrenal suppression.
Stress Dose Steroids ?
CASE REPORTS

FATAL ADRENAL CORTICAL INSUFFICIENCY PRECIPITATED
BY SURGERY DURING PROLONGED CONTINUOUS
CORTISONE TREATMENT*

By Leon Lewis, M.D., F.A.C.P., Berkeley, California, Robert F. Robinson,
M.D., Walnut Creek, California, James Yee, M.D., Oakland, California,
Lucy A. Hacker, M.D., and George Eisen, M.D.,
Vallejo, California

Annals Int Med, 1953
N = 40 renal Tx recipients on immunosuppressive prednisone (5-10 mg/day).

Admitted for infections, DKA, PE, surgery, etc.

No stress dose steroids.

No mortality, no incr length of stay, unexplained hypotension, other untoward events.

~ 60% with abnormal stim test
Hospitalized Patients on Exogenous Glucocorticoids

- Patients with Addison’s disease or known pituitary disease.
- Rare.
- Reasonable to temporarily increase GC (i.e., stress dose) in absence of data to the contrary.
Non-Critically Ill Patients on Exogenous Glucocorticoids

- Patients on chronic GC for other therapeutic reasons.
  - Stress dose steroids usually not necessary.
  - Adrenal stimulation tests usually not necessary.
    - If done, 250 ug cosyntropin test is probably good enough.
  - A peak cortisol around 18 ug/dL is adequate.
- Can usually be managed with clinical judgment.
Critically Ill Patients
Hypothalamus

CRH → Pituitary

ACTH → Adrenal Cortex

Cortisol

Stress
- hypotension
- fever
- trauma/surgery
- hypoglycemia
Serum Cortisol and Mortality

![Graph showing the relationship between basal cortisol levels and mortality.](image)
Total and Free Cortisol – ICU Patients

Hamrahian, NEJM 2004
Critical Illness Related Corticosteroid Insufficiency (CIRCI)

- Inadequate cellular corticosteroid activity for the severity of illness.
  - Inadequate GC production.
  - GC resistance at the cellular level.
- Reversible.
- Diagnosis problematic
  - Non-standard criteria
  - Random cortisol < 10 ug/dL or Δ cortisol < 9 ug/dL
Role of GC Therapy in CIRCI

Unclear.

Two major RCT with mortality endpoint - conflicting results.
Annane, et al, JAMA 2002

300 ICU patients in septic shock.

HC 200 mg/fludrocortisone 50 ug daily vs placebo.

250 ug cosyntropin stim test.

Primary outcome – 28 day mortality in non-responders (Δ cortisol < 9 ug/dL).
Mortality Rates

Mortality Day 28 (%)

- Placebo: 76%
- Steroids: 24%

P = 0.04

* Indicates statistical significance.
CORTICUS TRIAL
NEJM, 2008

- 499 ICU patients in septic shock.
- HC 200 mg daily vs placebo.
- 250 ug cosyntropin stim test.
- Primary outcome – 28 day mortality in non-responders.
Mortality Rates

Mortality Day 28 (%)

- Placebo: 36, 29, 31
- Steroids: 39, 29, 34

Nonresponders: 48%
Responders: 51%
All: 34%
Role of GC Therapy in CIRCI

Current recommendations (Surviving Sepsis Campaign, Amer College Critical Care Medicine)

- Septic shock not responding to fluids/pressors.
- GC replacement ~ 200 mg/day.
- Quality of evidence – moderate/low; strength of recommendation - weak.
Patients with Liver Disease
The Hepato-Adrenal Syndrome

- High prevalence of adrenal insufficiency reported in patients with liver failure.
  - 30% - 60% - acute liver failure, cirrhosis/sepsis, stable liver disease.

- Potential for large confounding due to effects of liver disease on protein levels.
Prevalence of Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Criteria</th>
<th>% AI</th>
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<tbody>
<tr>
<td>Any criteria</td>
<td>58%</td>
</tr>
<tr>
<td>Std</td>
<td>39%</td>
</tr>
<tr>
<td>CIRCI</td>
<td>47%</td>
</tr>
<tr>
<td>Free cortisol</td>
<td>12%</td>
</tr>
</tbody>
</table>

Tan, J Hepat, 2010
Hydrocortisone and Septic Shock Outcome in Cirrhosis

Arabi CMAJ 2010
Why Not Treat?
Fig. 4. Case 1. The original example (1902) of basophil (unverified) obesity.
Potential Adverse Effects of Stress Dose Steroids

- Hyperglycemia
- Infection
- Myopathy
- GI bleeding
- Adrenal suppression
Conclusions

- Signs/symptoms consistent with adrenal insufficiency are not uncommon in ill, hospitalized patients.
- Standard criteria for diagnosing adrenal insufficiency in the outpatient setting may not be valid in hospitalized patients, particularly severely ill patients.
- For patients on exogenous steroids for immunosuppression, adrenal suppression is expected. However, stress dose steroids are often not necessary during hospitalizations.
Conclusions

- Adrenal hemorrhage is a rare but life threatening cause of adrenal insufficiency in the hospital setting.
- Use of stress dose steroids in septic patients has not been clearly shown to be of benefit, particularly in patients with liver disease.
- The potential for stress dose steroids to cause harm must be weighed against possible benefits.
Endocrinology

Hypothalamus
Releasing hormones:
GHRH, CRH, TRH, GnRH
Inhibitory hormones:
somatostatin,
dopamine,
vasopressin,
prolactin

Pituitary gland
Growth hormone,
Prolactin
ACTH, MSH
TSH, FSH, & LH

Thyroid gland
T3, T4, & calcitonin

Parathyroid glands
Parathyroid hormone

Adrenal glands
Cortisol
Aldosterone
Adrenal androgens
Epinephrine
Noradrenaline

Pancreas
Insulin
Glucagon
Somatostatin

Ovaries
Estrogens
Progesterone

Testes
Testosterone

Source: Netter PE: Endocrine Physiology, 3rd Edition;
http://www.accessmedicine.com
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**Table 4. Cosyntropin-stimulation response**

<table>
<thead>
<tr>
<th>Cortisol levels (µg/dl)</th>
<th>%</th>
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<tbody>
<tr>
<td>Normal response</td>
<td>37</td>
</tr>
<tr>
<td>Baseline &lt;5</td>
<td>29</td>
</tr>
<tr>
<td>Increment &lt;6</td>
<td>17</td>
</tr>
<tr>
<td>Peak &lt;20</td>
<td>59</td>
</tr>
<tr>
<td>Increment &lt;6 and Peak &lt;20</td>
<td>12</td>
</tr>
</tbody>
</table>

*A normal cosyntropin stimulation response has a baseline >5 µg/dl, a peak >20 µg/dl, and an incremental change of >6 µg/dl. An increment of <6 µg/dl between the baseline and peak values is interpreted as mild-to-moderate adrenal dysfunction. A baseline <5 or a peak <20 is interpreted as moderate adrenal dysfunction. An increment <6 and a peak <20 are evidence of severe adrenal dysfunction.*
Basal Cortisol Predicts Stimulated Level

18 ug/dL
Cushing’s Signs and Symptoms

THE BASOPHIL ADENOMAS OF THE PITUITARY BODY
AND THEIR CLINICAL MANIFESTATIONS
(PITUITARY BASOPHILISM)

HARVEY CUSHING, M.D.
Professor of Surgery, Harvard Medical School

Introduction. In a long since superseded monograph on the pituitary body and its disorders, published in 1912, a section was devoted to a group of cases which showed peculiar and sundry polyglandular syndromes. It was stated at the time that the term “polyglandular syndrome” implied nothing more than that secondary functional alterations occur in the ductless-gland series whenever the activity of one of the glands becomes primarily affected; and further, that the term, as employed, was restricted to those cases in which it was difficult to tell where the initial fault lay.

Fig. 4. Case 1. The original example (1902) of basophil (unverified) obesity.
Cortisol Response after Cosyntropin vs Hypoglycemia

Lindholm, JCEM, 1978