Glycemic Control
Adrenal Insufficiency

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Introduction

- Glycemic Control
  - Issues
  - Hyper
  - Hypo
- Adrenal Insufficiency
  - Anatomy
  - Physiology
  - Issues
Stress Hyperglycemia

- Common following surgery, trauma, burns, and sepsis
- Strongly associated with poor outcomes
- Association appears stronger in non-diabetic patients than in diabetic patients
- Related to a state of insulin resistance (IR) that is promoted by stress related hormones and pro-inflammatory cytokines
Stress Hyperglycemia

- Infl Modulators
- Incr Adrenal response
- Proteolysis/Lipolysis
- Insulin Resistance
- Hyperglycemia
Insulin Resistance
Surgery/Critical Illness

• Biologic response
  • Decreased relative to normal
  • Significant variation
• Increases post-operatively in a dose-dep fashion
  • Based upon magnitude of operative intervention
  • Persists for several weeks
  • 50% increase after open cholecystectomy
Insulin Resistance
Surgery/Trauma/Burn/Sepsis

• Counter-regulatory hormones
  • Epinephrine, glucagon, cortisol, growth hormone

• Pro-inflammatory stimuli
  • NF\textsubscript{kβ}, TNF, IL-1, IL-6

• Defects in post-receptor insulin signaling
## Hyperglycemia

<table>
<thead>
<tr>
<th>Effects</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Endothelial dysfunction</td>
<td>• Renal failure</td>
</tr>
<tr>
<td>• Pro-inflammatory cytokines</td>
<td>• Polyneuropathy</td>
</tr>
<tr>
<td>• Platelet Activation</td>
<td>• Prolonged Mech Vent</td>
</tr>
<tr>
<td>• Procoagulation</td>
<td>• Transfusion increases</td>
</tr>
<tr>
<td>• Mitochondrial dysfunction</td>
<td>• Sepsis/Wound infection</td>
</tr>
<tr>
<td>• Acid/base changes</td>
<td>• Ischemia</td>
</tr>
<tr>
<td>• Immune dysregulation</td>
<td>• Arrhythmias</td>
</tr>
<tr>
<td>• Catabolism</td>
<td>• Nephropathy</td>
</tr>
</tbody>
</table>

*Dungan Lancet 2009*
Insulin Effects
Stress and Critical Illness

• Metabolic
  • Carbohydrate metabolism
  • Lipid metabolism
  • Protein metabolism

• Immunologic
  • Reduce pro-inflammatory cytokines
  • Enhance anti-inflammatory cytokines
  • Decrease complement (C3,C4) activation

Carlson GL. Ann R Coll Surg Engl 2004
Deng, H. Int. Immunopharmacology
Insulin

**Combat hyperglycemia**
- Conserve protein
- Decrease free fatty acid level

Reduce hypermetabolism

Inhibit inflammatory response
- Decrease inflammatory mediators
- Alleviating acute phase reaction of liver
- Protect endothelial cells
- Modulate expression of adhesion molecules
- Protect gut's integrity and GALT

Enhance immune competence
- Inhibit apoptosis of Mo/MΦ
- Increase total PMN accounts
- Improve chemotaxis and oxidative killing capacity of PMN
- Induce Th2 differentiation
- NK cells, CD4+CD25+ T cells, γδ T cells and NKT cells
Glucose Control

• Lowers risk of wound infection in diabetics
  • Cardiac patient population

• Reduced incidence of sternal infections

• Long-term survival benefit after AMI in diabetics (DIGAMI)

  Zerr *Ann Thorac Surg* 1997

  Furnary *Ann Thorac Surg* 1999

  Malmberg *BMJ* 1997
Major randomized studies of intensive insulin therapy (IIT) in critically ill patients


# Intensive Insulin Therapy Reduces Mortality In Critically Ill Surgical Patients

## Results

<table>
<thead>
<tr>
<th>Variable (%)</th>
<th>Control Group</th>
<th>Treatment Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV insulin Rx hypoglycemia (&lt; 40 mg/dl)</td>
<td>39</td>
<td>99</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>In-hosp. Mort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>10.9</td>
<td>7.2</td>
<td>0.01</td>
</tr>
<tr>
<td>ICU &gt; 5d</td>
<td>26.3</td>
<td>16.8</td>
<td>0.01</td>
</tr>
</tbody>
</table>

32% adjusted mortality reduction

Intensive Insulin Therapy Reduces Mortality In Critically Ill Surgical Patients

Van den Berghe G *NEJM* 2001
Meta-analysis of IIT critical illness

• All studies combined:
  • no significant benefit

• Surgical ICU studies:
  • significant benefit

Griesdale D *CMAJ* 2009
Meta-analysis of IIT critical illness

- All studies combined:
  - no significant benefit

- Surgical ICU studies:
  - significant benefit

30% Risk Reduction

Griesdale D CMAJ 2009
Summary of results - ITT vs Conventional:

- Older (10.8 vs 7.7 yrs)
- > 3rd degree (52 vs 44)
- ↓ sepsis (8.2% vs 22.6%)
- ↑ organ function (renal, hepatic)
- ↑ lean mass, body mass
- ↓ inflammatory response
- ↑ hypoglycemia (26% vs 9% < 40 mg/dl)
- Mortality 4% vs 11% (p = 0.14)

*(power analysis for 50% reduction, 3:1 randomization = 570 pts)*
IIT in critically ill surgical patients

Conclusions

• Plausible physiologic rationale for its benefit
• Weight of the data supports its benefit
• Many questions remain:
  • Optimum target range
  • Influence of hypoglycemia
  • Influence of timing and type of nutrition
  • Influence of patient factors: IR, variability, diabetes
Glycemic variability and mortality in critically ill


### Variables Associated with Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.03–1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.72</td>
<td>0.45–1.14</td>
<td>0.163</td>
</tr>
<tr>
<td>Penetrating trauma</td>
<td>0.38</td>
<td>0.22–0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ISS</td>
<td>1.03</td>
<td>1.01–1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shock_adm</td>
<td>0.75</td>
<td>0.51–1.11</td>
<td>0.151</td>
</tr>
<tr>
<td>Head AIS</td>
<td>1.40</td>
<td>1.23–1.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GCS_adm</td>
<td>0.90</td>
<td>0.86–0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.07</td>
<td>1.37–3.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BG_adm</td>
<td>1.00</td>
<td>0.99–1.00</td>
<td>0.741</td>
</tr>
<tr>
<td>BG_mean</td>
<td>1.00</td>
<td>1.00–1.01</td>
<td>0.05</td>
</tr>
<tr>
<td>BG_var</td>
<td>5.33</td>
<td>1.83–15.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mohr AM. Amer Surg. 2010; 8:896-902
Percent mortality by glycemic variability

Mohr AM. Amer Surg. 2010; 8:896-902
What about hypoglycemia?

Griesdale D. CMAJ 2009;180(8):821-827
What about hypoglycemia?

Favors Control

<table>
<thead>
<tr>
<th>Study</th>
<th>No. events / total no. patients</th>
<th>IIT</th>
<th>Control</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henderson et al.⁴¹</td>
<td>7/32</td>
<td>1/35</td>
<td>7.66 (1.00–58.86)</td>
<td></td>
</tr>
<tr>
<td>Bland et al.²⁵</td>
<td>1/5</td>
<td>1/5</td>
<td>1.00 (0.08–11.93)</td>
<td></td>
</tr>
<tr>
<td>Van den Berghe et al⁹</td>
<td>111/595</td>
<td>19/605</td>
<td>5.94 (3.70–9.54)</td>
<td></td>
</tr>
<tr>
<td>Mitchell et al.²⁵</td>
<td>5/35</td>
<td>0/35</td>
<td>11.00 (0.63–191.69)</td>
<td></td>
</tr>
<tr>
<td>Azevedo et al.²²</td>
<td>27/168</td>
<td>6/169</td>
<td>4.53 (1.92–10.68)</td>
<td></td>
</tr>
<tr>
<td>De La Rosa Gdel et al.¹²</td>
<td>21/254</td>
<td>2/250</td>
<td>10.33 (2.45–43.61)</td>
<td></td>
</tr>
<tr>
<td>Devos et al.¹³</td>
<td>54/550</td>
<td>15/551</td>
<td>3.61 (2.06–6.31)</td>
<td></td>
</tr>
<tr>
<td>Oksanen et al.²⁶</td>
<td>7/39</td>
<td>1/51</td>
<td>9.15 (1.17–71.35)</td>
<td></td>
</tr>
<tr>
<td>Brunkhorst et al.¹¹</td>
<td>42/247</td>
<td>12/290</td>
<td>4.11 (2.21–7.63)</td>
<td></td>
</tr>
<tr>
<td>Iapichino et al.²²</td>
<td>8/45</td>
<td>3/45</td>
<td>2.67 (0.76–9.41)</td>
<td></td>
</tr>
<tr>
<td>Arabi et al.¹⁹</td>
<td>76/266</td>
<td>8/257</td>
<td>9.18 (4.52–18.63)</td>
<td></td>
</tr>
<tr>
<td>Mackenzie et al.²³</td>
<td>50/121</td>
<td>9/119</td>
<td>5.46 (2.82–10.60)</td>
<td></td>
</tr>
<tr>
<td>NICE-SUGAR¹⁸</td>
<td>206/3016</td>
<td>15/3014</td>
<td>13.72 (8.15–23.12)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>654/6138</td>
<td>98/6209</td>
<td>5.99 (4.47–8.03)</td>
<td></td>
</tr>
</tbody>
</table>

Griesdale D. CMAJ 2009;180(8):821-827
Hypoglycemia
Cause of mortality or Result of Illness severity

Several studies demonstrate association of hypoglycemia with death:

• Krinsley JS - Severe hypoglycemia in critically ill patients: risk factors and outcomes
  *Crit Care Med.* 2007;35:2262-2267

Some studies demonstrate hypoglycemia associated with severity of illness and not an independent predictor of death:

• Arabi YM - Hypoglycemia with intensive insulin therapy in critically ill patients: predisposing factors and association with mortality
  *Crit Care Med.* 2009;37:2536-2544

• Mowery NT - Severe hypoglycemia while on intensive insulin therapy is not an independent predictor of death after trauma
  *J Trauma.* 2010;68:342-347
Effect of balanced nutrition on hypoglycemia

Insulin protocol:
- Mandates D10W @ 30 ml/hr if no nutritional source
- Examined risk of subsequent hypoglycemia (<50 mg/dl) for 2 hour blocks increments by glucose source

Rate of hypoglycemia:
- Pts with TPN / enteral: 2.2/1000
- Pts without TPN / enteral: 5.7/1000

Regression analysis -
- Significant predictors of hypoglycemia:
  - No TPN / enteral: OR 3.6
  - Age > 65: OR 1.5
- Not significant: APACHE II, diabetes, time on protocol
Predictors of Hypoglycemia:
regression analysis

- **Predictive**
  - Increased BG variability
  - Time since last BG measurement
  - Weight
  - Age
  - Previous low BG (<60 mg/dL)
  - Provision of balanced nutrition (tube feeds, TPN)

- **Not Predictive**
  - APACHE II
  - History of diabetes
  - Time on protocol
  - Hematocrit
  - WBC count
  - Heart rate
  - Time off unit
  - Pressor use
Only beginning to find the “truth” about glycemic control in critically ill surgical patients

- Stress hyperglycemia is a complex topic
- IIT in critically ill surgical patients provides outcome benefit
  - Optimum target unknown
- Outcomes and degree of IR are related
- Glucose variability, hypoglycemia, and outcome are related
- Influence of timing and type of nutrition inadequately understood
- Influence of patient factors remain unclear:
  - IR, variability, diabetes
Adrenal Insufficiency

Cortisol
Clinical Scenario

• 32 y male, MVC, unrestrained driver
  • Positive LOC, required intubation for agitation
    • Etomidate/succinylcholine RSI at scene

• CT: SAH, bilateral rib fractures, no solid organ

• ICU management
  • Arrive to the bedside
    • 30 mic/min levophed…
Figure AN-1: Hypothalamic-Pituitary-Adrenal (HPA) Axis

- Hypothalamus
- Releasing Factor
- Anterior Pituitary
- ACTH (through blood)
- Adrenal Cortex
- Cortisol
Anatomy-Output

- ADRENAL CORTEX
  - Zona glomerulosa - Aldosterone
  - Zona fasciculata - Cortisol
  - Zona reticularis - Androgens, Estrogens

- ADRENAL MEDULLA - Catecholamines
Physiologic Actions

Metabolic

- ↑ hepatic gluconeogenesis
- ↓ adipose tissue glucose uptake
- Stimulate free FA release via lipolysis
- Stimulate amino-acid release from protein
- Stimulate insulin release due to increased glucose production

Barseghian, Endocrinology 1982
Physiologic Actions
Cardiovascular

- ↑ transcription and expression of catecholamines and catecholamine receptors

- Inhibit production of nitric oxide

- Inhibit release of histamine from mast cells

Barseghian, *Endocrinology* 1982
Physiologic Actions

Immunologic

• Suppress cytokine production by inhibiting transcription factors
  • IL-1, 2, 3, 6, interferon-γ, TNF-α

• Enhance release of anti-inflammatory factors
  • IL-1 receptor antagonist, soluble TNF receptor, IL-10

• Increase release of neutrophils from bone marrow, inhibits migration from blood vessels

Barseghian, Endocrinology 1982
Adverse Reactions

- Fluid/electrolyte disturbances
  - Na+ retention, K+ loss
  - Fluid retention
- Osteoporosis
- Protein catabolism
  - Negative Nitrogen Balance
- Gastrointestinal
  - Peptic ulcer perforation
  - Pancreatitis
- Endocrine
  - Secondary HPA-axis inhibition
  - Diabetes
- Central Nervous System
  - Delirium???
- Infection
  - Estimated risk
    - 1.5 times control
SYNDROMES
Acute Insufficiency

• Severe/Acute illness
  • Intrinsic adrenal disease
  • Inadequate adrenal reserve
  • HIV, TB, primary autoimmune adrenalitis, chronic steroid administration
• HIV
  • # 1 primary adrenal insufficiency
  • Opportunistic infection/HIV virus
SYNDROMES

Acute Insufficiency

• A-Severe/Acute illness
  • Steroid administration
    • #1 secondary adrenal insufficiency
    • Recovery may take 9-12 months
  • 10 days
  • 5mg prednisone
  • Inhaled glucocorticoids
    • Azmacort
    • Beclovent
    • Flovent
    • Vanceril

• B-Adrenal hemorrhage
  • Rogoff’s sign
  • Blunt trauma
  • Coagulopathy
  • Pregnancy
SYNDROMES
Sub-acute Insufficiency

- Normal baseline function
- Common in septic ICU patients ?*
- Think adrenal insufficiency:
  - Volume-unresponsive/pressor-dependent
  - Unable to wean off low-dose pressors
  - Ventilator unresponsive

"High incidence of adrenocortical insufficiency in patients with the Multiorgan Dysfunction Syndrome". Polderman. University Hospital Vrije Universiteit.
## Adrenergic Pathology

<table>
<thead>
<tr>
<th></th>
<th>Plasma Cortisol</th>
<th>Plasma ACTH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Hypercortisolism</strong></td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Secondary Hypercortisolism</strong> (pituitary, Cushing's disease)</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Primary Hypocortisolism</strong> (Addison's disease)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Secondary Hypocortisolism</strong> (pituitary)</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
SIGNS/SYMPTOMS

- Shock
  - Hypovolemic
  - Hyperdynamic
- $\downarrow$ Na
- $\uparrow$ K
- Metabolic acidosis
- Hypoglycemia
- Eosinophilia
Cortisol with Stress

Lamberts, NEJM 1997
### All-Cause Mortality at 28 Days

#### Short Course, High Dose

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klastersky 1971</td>
<td>B-meth 1mg/kg/day x 2doses for 3d; Placebo</td>
</tr>
<tr>
<td>Schumer 1976</td>
<td>Dex 3mg/kg; M-pred 30mg/kg; Placebo – repeat x1 in 4hrs</td>
</tr>
<tr>
<td>Lucas 1984</td>
<td>Dex 2mg/kg, 2mg/kg/24h x 2d</td>
</tr>
<tr>
<td>Sprung 1984</td>
<td>Dex 6mg/kg; M-pred 30mg/kg; Placebo – repeat x1 in 4hrs</td>
</tr>
<tr>
<td>Bone 1987</td>
<td>M-pred 30mg/kg; Placebo</td>
</tr>
<tr>
<td>VASSCSG 1987</td>
<td>M-pred 30mg/kg, 5mg/kg/hr x 9hrs</td>
</tr>
<tr>
<td>Luce 1988</td>
<td>M-pred 30mg/kg q6h x 24hrs; Placebo</td>
</tr>
<tr>
<td>Slusher 1996</td>
<td>Dex 0.2 mg/kg q8h x 2d; Placebo</td>
</tr>
</tbody>
</table>

## All-Cause Mortality at 28 Days

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight</th>
<th>RR (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klastersky 1971</td>
<td>22/46</td>
<td>18/39</td>
<td>11.47%</td>
<td>1.04 (0.66 to 1.63)</td>
</tr>
<tr>
<td>Schumer 1976</td>
<td>9/86</td>
<td>33/86</td>
<td>19.43%</td>
<td>0.27 (0.27 to 0.53)</td>
</tr>
<tr>
<td>Lucas 1984</td>
<td>5/23</td>
<td>5/25</td>
<td>2.82%</td>
<td>1.09 (0.36 to 3.27)</td>
</tr>
<tr>
<td>Sprung 1984</td>
<td>33/43</td>
<td>11/16</td>
<td>9.44%</td>
<td>1.12 (0.77 to 1.61)</td>
</tr>
<tr>
<td>Bone 1987</td>
<td>65/191</td>
<td>48/190</td>
<td>28.34%</td>
<td>1.35 (0.98 to 1.84)</td>
</tr>
<tr>
<td>VASSCSG 1987</td>
<td>23/112</td>
<td>24/111</td>
<td>14.20%</td>
<td>0.95 (0.57 to 1.58)</td>
</tr>
<tr>
<td>Luce 1988</td>
<td>22/38</td>
<td>20/37</td>
<td>11.94%</td>
<td>1.07 (0.72 to 1.60)</td>
</tr>
<tr>
<td>Slusher 1996</td>
<td>6/36</td>
<td>4/36</td>
<td>2.36%</td>
<td>1.50 (0.46 to 4.87)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>575</strong></td>
<td><strong>540</strong></td>
<td><strong>100%</strong></td>
<td><strong>0.99 (0.83 to 1.17)</strong></td>
</tr>
</tbody>
</table>

Adrenal Insufficiency in Septic Shock

- Turney 1987
  - Pts w/cortisol levels (> 60 μg/dl) had ↑ mortality, compared to pts who stimulated > 18 μg/dl after ACTH injection had improved outcomes

- Rothwell 1991
  - 32 pts with septic shock
    - 13 exhibited cortisol response (≤9 μg/dl) all of whom died

- Moran 1995
  - Regression analysis predicted ↑ mortality by ↑ cortisol and onset of shock

- Soni 1995
  - Mortality in pts w/Al was 80% at 4 weeks as compared to 43.8% in pts with normal adrenal response.
Etomidate is the Devil

**Desmolase**  
Cholesterol ➔ **Pregnenolone** ➔ **170H-Pregnenolone** ➔ Dehydroepiandrosterone

<table>
<thead>
<tr>
<th>3β Hydroxysteroid dehydrogenase (3βHSD)</th>
<th>3βHSD</th>
<th>3βHSD</th>
</tr>
</thead>
</table>

**Progesterone** ➔ **170H-Progesterone** ➔ Androstenedione

<table>
<thead>
<tr>
<th>21-Hydroxylase</th>
<th>21-Hydroxylase</th>
<th>Peripheral tissues</th>
</tr>
</thead>
</table>

**Deoxycorticosterone** ➔ **11-Deoxycortisol** ➔ Testosterone

<table>
<thead>
<tr>
<th>11β Hydroxylase</th>
<th>11β Hydroxylase</th>
</tr>
</thead>
</table>

**Corticosterone** ➔ **Cortisol**

<table>
<thead>
<tr>
<th>18-Hydroxylase</th>
<th>18-Oxidase</th>
</tr>
</thead>
</table>

**Aldosterone**

---

de Jong FH et al. 1984
Cortisol Response to Corticotropin in Septic Shock

- 189 consecutive patients with septic shock

- Intervention:
  - 0.25mg tetracosactrin
  - Cortisol samples taken at T₀, T₃₀, and T₆₀

- Outcome Measures:
  - 28-day mortality as a function of variables collected at onset of septic shock

Annane JAMA 2000.
Cortisol Response to Corticotropin in Septic Shock

- Mortality Outcomes
  - 109 (58%) died within 28 days
  - Median time to death was 17 days

- Median Cortisol at $T_0$
  - All patients – 34 µg/dl
  - Survivors – 28 µg/dl
  - Non-survivors – 39 µg/dl

Annane JAMA 2000.
Cortisol Response to Corticotropin in Septic Shock

Annane, JAMA 2000
Cortisol Response to Corticotropin in Septic Shock

- Median Time to Death
  - Baseline Cortisol $>34$ μg/dl
    - 6 days (95% CI 4-12 days)
  - Cortisol ΔMax $\leq 9$ μg/dl
    - 11 days (95% CI 8-15 days)
  - Baseline Cortisol >34 AND ΔMax $\leq 9$
    - 5 days (95% CI 2-12 days)

Annane JAMA 2000
## All-Cause Mortality at 28 Days

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bollaert 1998</strong></td>
</tr>
<tr>
<td>HC 100mg q8h x5d, taper over 6d</td>
</tr>
<tr>
<td><strong>Briegel 1999</strong></td>
</tr>
<tr>
<td>HC 100mg, 0.18mg/kg/hr, ↓ 0.08mg/kg/hr x6d at shock resolution. Tapered by 24mg/day by infection resolution or when sodium &gt;155mmol/L</td>
</tr>
<tr>
<td><strong>Chawla 1999</strong></td>
</tr>
<tr>
<td>HC 100mg q8h x72h, taper over 4d</td>
</tr>
<tr>
<td><strong>Yildiz 2002</strong></td>
</tr>
<tr>
<td>Pred 5mg at 0600, 2.5mg at 1800 x10d</td>
</tr>
<tr>
<td><strong>Annane 2002</strong></td>
</tr>
<tr>
<td>HC 50mg q6h + fludrocortisone 50μg tab qd x 7d</td>
</tr>
</tbody>
</table>

*Annane BMJ 2004*
## All-Cause Mortality at 28 Days

### Long Course, Low Dose

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight</th>
<th>RR (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bollaert 1998</td>
<td>7/22 (32%)</td>
<td>12/19 (63%)</td>
<td>9.84%</td>
<td>0.50 (0.25 to 1.02)</td>
</tr>
<tr>
<td>Briegel 1999</td>
<td>3/20 (15%)</td>
<td>4/20 (20%)</td>
<td>3.05%</td>
<td>0.75 (0.19 to 2.93)</td>
</tr>
<tr>
<td>Chawla 1999</td>
<td>6/23 (26%)</td>
<td>10/21 (48%)</td>
<td>7.98%</td>
<td>0.55 (0.24 to 1.25)</td>
</tr>
<tr>
<td>Yildiz 2002</td>
<td>8/20 (40%)</td>
<td>12/20 (60%)</td>
<td>9.16%</td>
<td>0.67 (0.35 to 1.27)</td>
</tr>
<tr>
<td>Annane 2002</td>
<td>82/151 (54%)</td>
<td>91/149 (61%)</td>
<td>69.96%</td>
<td>0.89 (0.73 to 1.08)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>236</td>
<td>229</td>
<td>100%</td>
<td><strong>0.80 (0.67 to 0.95)</strong></td>
</tr>
</tbody>
</table>

Annane *BMJ* 2004
Low Dose Hydrocortisone and Fludrocortisone & Mortality in Septic Shock

- 300 pts with septic shock

- **Intervention:**
  - All pts underwent cort-stim
  - Randomized to HC 50mg q6h + fludrocortisone 50μg tab qd x 7d or placebo

- **Primary Endpoint:**
  - 28-day survival distribution in pts w/relative adrenal insufficiency (non-responders) compared to responders
Low Dose Hydrocortisone and Fludrocortisone & Mortality in Septic Shock

- Outcomes:
  - 229 non-responders
  - 70 responders

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Corticosteroid</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>53%</td>
<td>61%</td>
<td>(.96)</td>
</tr>
<tr>
<td>Non-responders</td>
<td>63%</td>
<td>53%</td>
<td>(.04)</td>
</tr>
<tr>
<td>All</td>
<td>61%</td>
<td>55%</td>
<td>(.09)</td>
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Low Dose Hydrocortisone and Fludrocortisone & Mortality in Septic Shock

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  - 70 responders

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<td>55%</td>
<td>.09</td>
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</table>
Serum Free Cortisol

- Corticosteroid Levels in Serious Illness
  - Low Albumin Grp 1: 36
  - Normal Albumin Grp 2: 30
  - Healthy Volunteers Grp 3: 33
- Apache III scores > 15
- Stim Test 2p – 6p
  - Serum Total Cortisol
  - Aldosterone
  - Free Cortisol Levels

Hamrahian, JAMA 2004
Serum Free Cortisol

Table 1. Characteristics of Critically Ill Patients and Healthy Volunteers.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (N=36)</th>
<th>Group 2 (N=30)</th>
<th>Healthy Volunteers (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.2±14.2 †</td>
<td>66.9±10.9 †</td>
<td>54.6±16.6</td>
</tr>
<tr>
<td>Plasma corticotropin (ng/liter)‡</td>
<td>38.7±12.9 ‡</td>
<td>37.8±18.8 ‡</td>
<td>24.9±9.8</td>
</tr>
<tr>
<td>Corticosteroid-binding globulin (mg/liter)</td>
<td>17.7±5.9 ‡</td>
<td>21.4±6.8 ‡</td>
<td>26.0±3.8</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>1.9±0.3 ‡ ‡</td>
<td>3.1±0.4 ‡</td>
<td>3.9±0.3</td>
</tr>
<tr>
<td>Total serum protein (g/dl)</td>
<td>4.7±0.8 ‡ ‡</td>
<td>6.0±1.0 ‡</td>
<td>6.8±0.3</td>
</tr>
<tr>
<td>Duration of hospitalization before testing (days)</td>
<td>21.2±16.2 ‡ ‡</td>
<td>6.4±5.6</td>
<td>NA</td>
</tr>
<tr>
<td>Severity-of-illness score</td>
<td>41.6±15.8</td>
<td>40.6±21.4</td>
<td>NA</td>
</tr>
<tr>
<td>No. died/no. survived</td>
<td>12/24</td>
<td>7/23</td>
<td>NA</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>78±9</td>
<td>81±11</td>
<td>82±5</td>
</tr>
</tbody>
</table>
Serum Free Cortisol

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (N=36)</th>
<th>Group 2 (N=30)</th>
<th>Healthy Volunteers (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cortisol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line (µg/dl)</td>
<td>15.8±7.4† † † †</td>
<td>22.6±8.9† † † †</td>
<td>8.6±4.2</td>
</tr>
<tr>
<td>Range</td>
<td>5.3–35.4</td>
<td>9.6–54.0</td>
<td>3.8–23.7</td>
</tr>
<tr>
<td>Median</td>
<td>13.3</td>
<td>21.5</td>
<td>7.9</td>
</tr>
<tr>
<td>After cosyntropin stimulation (µg/dl)</td>
<td>23.4±9.5 § §</td>
<td>34.4±10.3</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>10.0–50.2</td>
<td>20.0–59.8</td>
<td>19.1–43.3</td>
</tr>
<tr>
<td>Median</td>
<td>21.2</td>
<td>31.6</td>
<td>27.2</td>
</tr>
<tr>
<td>Subjects with a maximal response &lt;18.5 µg per deciliter after cosyntropin stimulation — no./total no. (%)</td>
<td>14/36 (39) † † †</td>
<td>0/30</td>
<td>0/33</td>
</tr>
<tr>
<td><strong>Free cortisol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line (µg/dl)</td>
<td>5.1±4.1† † † **</td>
<td>5.2±3.5† † †</td>
<td>0.6±0.3</td>
</tr>
<tr>
<td>Range</td>
<td>1.3–12.8</td>
<td>1.5–13.0</td>
<td>0.2–1.4</td>
</tr>
<tr>
<td>Median</td>
<td>4.0</td>
<td>4.7</td>
<td>0.6</td>
</tr>
<tr>
<td>After cosyntropin stimulation (µg/dl)</td>
<td>9.3±6.3† † † † **</td>
<td>10.1±5.9† † †</td>
<td>2.8±0.7</td>
</tr>
<tr>
<td>Range</td>
<td>3.1–29.4</td>
<td>4.0–29.1</td>
<td>1.9–4.5</td>
</tr>
<tr>
<td>Median</td>
<td>8.6</td>
<td>9.2</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Cosyntropin-stimulated serum total cortisol and free cortisol concentrations are higher in critically ill patients than in healthy volunteers.
Serum Free Cortisol

• Conclusions:
  • base-line serum free cortisol 2.0 µg/dL
    • Low end level in healthy volunteers
    • threshold patients at risk for AI during critical illness
  • Free cortisol not correlated with mortality, yet
  • Glucocorticoid-resistance may be present
    • Therefore higher values still shows signs of AI

JAMA 2004
Adrenal Function

- Annane
  - 477 pts
  - ACTH stim test on day diagnoses septic
  - Non-survivors higher baseline cortisol
    - 29.5 ± 33.5 vs. 24.3 ± 16.5 g/dL, p=0.03
  - Similar peak levels
    - 37.6 ± 40.2 vs. 35.2 ± 22.9 g/dL, p=0.42

CCM 2007
Adrenal Function

- Baseline cortisol $<15$ g/dL or a max $<9$ g/dL
  - likelihood ratio of dying of 1.26
    - (95% confidence interval, 1.11–1.44)
  - longer duration of shock
  - a shorter survival time
- Max $<9$ g/dL with any baseline cortisol value
  - likelihood ratio of dying of 1.38
    - (95% confidence interval, 1.18 –1.61).

CCM 2007
# Odds of Poor Outcome, Controlling for Confounders

Logistic Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pneumonia</th>
<th>BSI</th>
<th>UTI</th>
<th>Other Infection</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid use</td>
<td>2.64 (1.21-5.76)*</td>
<td>3.25 (1.26-8.38)*</td>
<td>2.32 (0.95-5.68)</td>
<td>2.58 (0.87-7.67)†</td>
<td>1.89 (0.82-4.40)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>1.07 (1.00-1.13)*</td>
<td>1.04 (0.97-1.11)</td>
<td>1.04 (0.97-1.11)</td>
<td>1.03 (0.95-1.11)</td>
<td>1.16 (1.08-1.25)*</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.98-1.03)</td>
<td>1.00 (0.98-1.04)</td>
<td>0.99 (0.97-1.02)</td>
<td>0.98 (0.95-1.00)</td>
<td>1.04 (1.01-1.07)*</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>4.16 (1.00-17.26)*</td>
<td>2.64 (0.56-12.41)</td>
<td>0.76 (0.09-6.62)</td>
<td>1.34 (0.15-12.32)</td>
<td>0.24 (0.02-2.93)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.02 (0.55-7.47)</td>
<td>1.10 (0.25-4.82)</td>
<td>0</td>
<td>0</td>
<td>0.20 (0.02-1.90)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.71 (0.23-2.16)</td>
<td>0.75 (0.22-2.55)</td>
<td>1.51 (0.43-5.22)</td>
<td>0</td>
<td>0.83 (0.25-2.74)</td>
</tr>
<tr>
<td>Other medical conditions</td>
<td>1.13 (0.41-3.08)</td>
<td>2.40 (0.82-7.08)</td>
<td>0.81 (0.23-7.81)</td>
<td>0</td>
<td>0.33 (0.10-1.11)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BSI, bloodstream infection; CI, confidence interval; OR, odds ratio; UTI, urinary tract infection.

*P<.05.
†P<.10.

Britt, Arch Surg 2006
### Table 5. Chance of Longer LOS, Controlling for Confounders, Expressed as Slope of Regression Line

<table>
<thead>
<tr>
<th>Variable</th>
<th>ICU LOS</th>
<th>Ventilator LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid use</td>
<td>7.35*</td>
<td>5.05*</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>0.29†</td>
<td>0.32‡</td>
</tr>
<tr>
<td>Age</td>
<td>0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>2.06</td>
<td>-0.49</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-6.49</td>
<td>-4.98†*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.64</td>
<td>-0.92</td>
</tr>
<tr>
<td>Other Infection</td>
<td>3.41</td>
<td>-1.41</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; LOS, length of stay.

*P<.05.
†P<.10.
‡P<.01.

Britt, Arch Surg 2006
<table>
<thead>
<tr>
<th>Variable</th>
<th>ICU LOS</th>
<th>Ventilator LOS</th>
</tr>
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<tbody>
<tr>
<td>Steroid use</td>
<td>7.35*</td>
<td>5.05*</td>
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<td>APACHE II score</td>
<td>0.29†</td>
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<td>Age</td>
<td>0.04</td>
<td>0.06</td>
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<td>Pulmonary disease</td>
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<td>Diabetes</td>
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<td>-4.98†*</td>
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<tr>
<td>Hypertension</td>
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<td>-0.92</td>
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<tr>
<td>Other Infection</td>
<td></td>
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</table>

Abbreviations: APACHE II; ICU, intensive care unit; LOS, length of stay.
*P < .05.
†P < .10.
‡P < .01.

Britt, Arch Surg 2006
Current Opinion

Corticus

• ‘Hydrocortisone Therapy for Patients with Septic Shock’
  • Multicenter, randomized, double-blind, placebo-controlled
  • 499 pts
  • 251: 50mg Hydrocortisone every 6 hrs for 5 days
  • 248: placebo

• Primary Outcome:
  • Death in those that had no response to corticotropin test

NEJM 2008
Current Opinion

• Results:
  • 233 Pts without response
    • 125 Hydrocortisone group
    • 81 placebo
  • 28 day mortality- no difference
  • Overall mortality-NO DIFFERENCE
    • 86/251 (34.3%) Hydrocortisone group
    • 78/248 (31.5%) Placebo group

NEJM 2008
Current Opinion

• Interesting Findings:
  • 12% dopamine use
  • 10% epinephrine use
  • 8% activated protein c

• Responders: decrease time to reversal of shock

• SOFA score 10.6 ± 3.2
  • Mortality rate of 10%

• Increased risk of ‘super infections’
  • OR 1.37 (95% CI, 1.05-1.97)

• Increased Hyperglycemia
  • OR 1.18 (95% CI, 1.07-1.31)

NEJM 2008
Current Opinion

• Limitations
  • Underpowered (needed 800)
  • 52 European Centers
  • Etomidate in 26% of patients-with unresponsiveness

• Clinical Significance
  • Super infection 33 v 26 pts
  • Hyperglycemia >150 at any point in first seven days
    • 85 v 72 pts

NEJM 2008
Critical Illness-related Corticosteroid Insufficiency “CIRCI”

- Inadequate corticosteroid activity for the level of severity of illness
  - 20-60% adrenal insufficiency in critical illness
  - Due to corticosteroid tissue resistance AND low levels of free cortisol

Marik, *CHEST*, 2009
CIRCI
Clinical Manifestations

• Predicated on exaggerated pro-inflammatory immune response
  • Hypotension refractory to fluids
  • Requirement of pressors
  • Hyperdynamic profile (Sepsis-like)
    or
• Progressive ARDS with supportive care

Marik, CHEST, 2009
CIRCI
Treatment

• Steroid replacement therapy
  • NO ACTH stimulation test necessary
  • 50 mg every 6 hrs at least 7 days
    • May be up to 14 days
  • Taper when OFF pressors/ventilator

• Surveillance
  • Infection
  • Hyperglycemia

Marik, *CHEST*, 2009
What does it all mean?

• Adrenal insufficiency not present
  • Steroids are not beneficial

• Adrenal Insufficiency present
  • Chose the correct group to study/treat:
    • Low cortisol value
    • Low stim value
    • Pressors/Ventilator dependant
  • If steroids work, beneficial
  • If steroids don’t work, not beneficial
Glycemic Control
Adrenal Insufficiency

Oscar Guillamondegui, MD, MPH, FACS
Division of Trauma & Surgical Critical Care
Vanderbilt University Medical Center