Endocrine and Metabolic Complications in the ICU

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New Progress

- Discovery of complex neuro-endocrine adaptation to critical illness
- Leading to new insights and major breakthroughs in the field of critical care
Areas to cover

- Cortisol
- Insulin
- Prognostic indices
Areas to cover

• Cortisol
• Insulin
• Prognostic indices
So what happens in septic shock?

• Critically ill patients generally have elevated cortisol levels
• Some appear to have inadequate cortisol activity in relation to the severity of their disease
Hypothesis

• Corticosteroid treatment may improve survival in septic shock
• Early studies showed this to be true in various experimental animal models
Study results in humans

• No benefit (actually harm) from large-dose steroids early in sepsis
• Methylprednisolone 30 mg/kg
• Side effects of high dose steroids
  – GI bleeding
  – Secondary infections
  – Steroid psychosis
Meta-analyses

• 2 published in 1995
• High dose steroids in sepsis or septic shock
• No significant difference in absolute mortality or relative risk of death
• But significant heterogeneity across the trials due to dosages, timing, duration
Annane et al - 2002

- Randomized, placebo controlled, prospective trial
- 300 patients
- 19 participating French ICUs
- Hydrocortisone 50 mg every 6 hours and fludrocortisone 50 mcg/d x 7 days
- Low dosages and longer time periods
Responders vs. Non-responders

250 mcg Corticotropin, blood samples at 30 and 60 minutes

<table>
<thead>
<tr>
<th>Response to corticotropin</th>
<th>Category</th>
<th># of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;9 mcg/ dL</td>
<td>Responder</td>
<td>70/300 (23%)</td>
</tr>
<tr>
<td>&lt;9 mcg/dL</td>
<td>Nonresponder</td>
<td>230/300 (77%)</td>
</tr>
</tbody>
</table>

Annane et al, JAMA, 288; 2002
## Results

<table>
<thead>
<tr>
<th></th>
<th>Nonresponder</th>
<th>Responders</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Steroid</td>
<td>Placebo</td>
</tr>
<tr>
<td># patients</td>
<td>115</td>
<td>114</td>
<td>34</td>
</tr>
<tr>
<td>28d mortality</td>
<td>63%</td>
<td>53%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Annane et al, JAMA, 288; 2002
More recent meta-analysis

• Meta-analysis published in 2004 and Cochrane database
• Analyzed trials after 1997
  – Standardized definition of severe sepsis and septic shock
  – Different steroid dose (low dose and longer duration)

  Minneci et al, Ann Intern Med, 141; 2004
  Annane et al, Cochrane Collaboration, 2005
Results

• Relative risk of dying at 28 days 0.8 (95% CI 0.67-0.95, p=0.01)
• Relative risk of dying in hospital 0.83 (95% CI 0.71-0.97, p=0.02)
• No heterogeneity
• No increased incidence of GI bleeding, superinfection, hyperglycemia
### Results

**Summary**

<table>
<thead>
<tr>
<th>Category</th>
<th>Count (n)</th>
<th>Events (N)</th>
<th>Survival Benefit (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies (n = 13)</td>
<td>875 (357)</td>
<td>842 (339)</td>
<td>1.01 (0.94–1.09)</td>
</tr>
<tr>
<td>Pre-1989 studies with reference 16 (n = 9)</td>
<td>663 (257)</td>
<td>634 (220)</td>
<td>0.97 (0.89–1.04)</td>
</tr>
<tr>
<td>Pre-1989 studies without reference 16 (n = 8)</td>
<td>577 (248)</td>
<td>548 (187)</td>
<td>0.89 (0.82–0.97)</td>
</tr>
<tr>
<td>Post-1997 studies (n = 4)</td>
<td>212 (100)</td>
<td>208 (119)</td>
<td>1.23 (1.01–1.50)</td>
</tr>
</tbody>
</table>

Minneci et al, Ann Intern Med, 141; 2004
Results

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Relative Shock Reversal Benefit (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bollaert et al., 1998 (31)</td>
<td>3.24 (1.50–7.01)</td>
</tr>
<tr>
<td>Briegel et al., 1999 (32)</td>
<td>1.13 (0.86–1.46)</td>
</tr>
<tr>
<td>Chawla et al., 1999 (33)</td>
<td>2.09 (1.14–3.83)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Hazard Ratio for Shock Reversal (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane et al., 2002 (30)</td>
<td>1.54 (1.10–2.16)</td>
</tr>
</tbody>
</table>

Minneci et al, Ann Intern Med, 141; 2004
Cortisol levels

≤15 mcg/dL  

Adrenal Failure  
Replace

Stimulation Test  
≥15 mcg/dL  
Rise ≥ 9 mcg/dL

Cortisol  
> 15 mcg/dL  
< 34 mcg/dL

No Treatment

Cortisol  
> 34 mcg/dL

Tissue Resistance

Rise ≤ 9 mcg/dL
Is Annane the final answer?

• Objective: assess whether low-dose corticosteroid improves survival in pts with septic shock and sepsis

• Setting: 52 ICUs in multiple European countries (2002-2005)

Brunkhorst et al, NEJM, 358, 2008
Corticus Study

• Enrolled: 499/800
  – Slow recruitment
  – Termination of funding
  – Expiration of trial drug

• Steroid Taper (HC 300 mg/d x 5d, 100 mg/d x 3d, 50 mg/d x 3d)

• No mineralocorticoid

• 233 (46.7%) did not have response to corticotropin (vs. 77% Annane)
## Corticus Results

<table>
<thead>
<tr>
<th></th>
<th>28-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>39.2%</td>
</tr>
<tr>
<td>Annane</td>
<td>53%</td>
</tr>
<tr>
<td>Responders</td>
<td>28.8%</td>
</tr>
<tr>
<td>Total</td>
<td>34.3%</td>
</tr>
</tbody>
</table>
Corticus - Results

• Shock reversed more quickly in hydrocortisone group (3.3d vs. 5.8d)

• More adverse events
  – New sepsis/shock (OR 1.37)
  – Hyperglycemia
Pendulum trend - future implications

• Criteria for adrenal insufficiency in septic shock remains to be defined
• Optimal timing, dose, duration, withdrawal, +/- mineralocorticoids
Further research implications

• Studies are inadequately powered
  – 15% reduction in relative risk from a mortality of 35%
  – Requires 2600 patients

• Vasopressor weaning is unreliable surrogate outcome
Etomidate

- Carboxylated imidazo
- Benefits
  - Provides relative hemodynamic stability for level of sedation
  - Limited suppression of ventilation
  - Lack of histamine release
  - Available in prefilled syringes
Most importantly…
Steroid synthesis

pregnenolone

17-hydroxy pregnenolone

NADPH + O₂ → NADH

progesterone

17-hydroxyprogesterone

NADPH + O₂ 21-hydroxylase

11-deoxycortisol

NADPH + O₂

11β-hydroxylase

corticosterone

cortisol or hydrocortisone®
Problems

- Interferes with adrenal function
- Single doses shown to cause short-lived suppression of cortisol synthesis
- <12 to 24 hours of transient adrenocortical suppression
- Clinical significance in healthy patients undergoing minor procedures
Septic shock and Etomidate

- Retrospective
- 152 pts with septic shock
- Adrenal insufficiency definition:
  - < 9 mcg/dL rise in serum cortisol with cortisol stimulation test (250 mcg)
Results

• Incidence of adrenal insufficiency:
  – 76% in etomidate group
  – 51% in other group

• Median time interval between etomidate and cort stim test 7 (4-10 hours)
Corticus - Etomidate

• Etomidate used in ~26%
• Of those, 60% nonresponders
• Increased 28 d mortality in patients who received etomidate (45.1% vs. ~30%) - regardless of HC or placebo
• OR 1.82 (CI 0.52 - 6.36) for mortality
Conclusion for etomidate

- Potential for harm must be weighed against its benefits
- Etomidate is more hemodynamically stable
- In patients with septic shock, the incidence of adrenal insufficiency after etomidate induction is reported to be quite high
Choices

• Use etomidate with automatic administration of corticosteroids
  – Dose and timing would be speculative
• Use subanesthetic doses of etomidate as adjunct to allow for lower doses of another agent
• Eliminate use of etomidate for septic shock
Areas to cover

- Cortisol
- Insulin
- Prognostic indices
Hyperglycemia

- Stress of critical illness leads to increased catecholamines
  - Defective suppression of gluconeogenesis
  - Resistance to the peripheral actions of insulin
- Prolonged in pts with continued tissue hypoperfusion or persistent infection
- Leads to multisystem organ failure and death
Prior clinical practice

- Treat glucose > 200 mg/dL
- Goals 160-200 mg/dL
- SQ insulin
- Insulin infusions
What’s been proven harmful about hyperglycemia?

- Increased rate of postoperative infections (especially cardiac surgery)
- Poor prognosis in patients with stroke or head injury
- Decreased survival in diabetics after MI
Van den Berghe et al - 2001

- Prospective randomized trial
- 1548 patients admitted to surgical ICU
- >60% were cardiac surgery pts
- Control: glucose 180-200 mg/dL (10-11 mmol/L)
- Intervention: glucose 80-100 mg/dL (4.4-6.1 mmol/L)
Adverse Effects

• Hypoglycemia (40 mg/dL) occurred in 39 patients (5%) in intervention group vs. 6 (<1%) patients in control group
• Associated symptoms: sweating and agitation
• No instances of hemodynamic deterioration or convulsions
## Results

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU mortality</td>
<td>8%</td>
<td>4.6%</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Mortality &gt;5d ICU stay</td>
<td>20.2%</td>
<td>10.6%</td>
<td>0.005</td>
</tr>
<tr>
<td>Infections</td>
<td>7.8%</td>
<td>4.2%</td>
<td>0.003</td>
</tr>
<tr>
<td>Renal failure</td>
<td>8.2%</td>
<td>4.8%</td>
<td>0.007</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>51.9%</td>
<td>28.7%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Results

A: Survival in ICU (%)

B: In-Hospital Survival (%)

Days after Admission

Intensive treatment

Conventional treatment
Is it the glucose or the insulin?

- Insulin inhibits TNF$_\alpha$
- TNF$_\alpha$
  - Triggers procoagulant activity
  - Fibrin deposition
  - Inhibits macrophage inhibitory factor
    - Contributes to endotoxemia and shock
Hyperglycemia vs. low insulin

- Finney et al
- 523 mostly surgical ICU patients
- Prospective observational study

Finney et al, JAMA 290, 2003
Hypercglycemia vs. low insulin

- Primary determinant of poor outcome was hyperglycemia not hypoinsulinemia
- Increased insulin dosing led to increased mortality across all ranges of glycemia
- Regression model suggested mortality benefit below a target glucose level of only < 145 mg/dL
Applicability to all ICU patients

• 1200 patients with predicted ICU stay > 3 days
  
• Intensive treatment group
  – Insulin started when glucose > 110 mg/dL
  – Titrated to keep glucose between 80-110 mg/dL

• Conventional group
  – Insulin started when glucose > 215 mg/dL
  – Titrated to keep glucose between 180-200 mg/dL
Results

• Reduced morbidity
  – Reduction in newly acquired renal injury
  – Earlier wean from mechanical ventilation
  – Earlier discharge from ICU and hospital

• No difference in mortality
  – 40% (conventional) vs. 37.3% (insulin)(in-hospital)
  – 26.8% vs. 24.2% (in ICU)

Van den Berghe et al, NEJM, 354, 2006
Patients in ICU for ≥ 3 days

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Conventional</th>
<th>Tight control</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital</td>
<td>52.5%</td>
<td>43%</td>
</tr>
<tr>
<td>In-ICU</td>
<td>38.1%</td>
<td>31.3%</td>
</tr>
</tbody>
</table>
Conclusion

• Unclear if intensive insulin therapy for < 3 days causes harm
• Maybe benefit from intensive insulin therapy requires time to be realized
• So that benefits of tight glucose control outweigh initial risks from hypoglycemia
# Adverse Effects - hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Intensive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>3.1%</td>
<td>18.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ICU &gt; 3 days</strong></td>
<td>3.9%</td>
<td>25.1%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Adverse Effects - hypoglycemia

• VISEP
  – Volume Substitution and Insulin Therapy in Severe Sepsis
  – Stopped after 488/600 patients
  – Hypoglycemia (12.1% vs. 2.1%, p<0.001)

• GLUCONTROL
  – Comparing the Effects of Two Glucose Control Regimens by Insulin in ICU Patients
  – Stopped after 1101/3500
  – Hypoglycemia (8.6% vs. 2.4%, p<0.001)
NICE-SUGAR study
NICE-SUGAR

• Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation
• Endpoints - 90 day mortality
• Enrolled 4000/6000 patients
• 2 groups
  – Glucose 80-100 mg/dL
  – Glucose 140-180 mg/dL
Conclusion

• Withhold intensive insulin for more data
• Administer insulin to all ICU patients on assumption that more pts will benefit than be harmed
• Maybe don’t need to be as “tight” as 80-100 mg/dL, but < 150 mg/dL is acceptable
Insulin protocols

- Boluses of insulin
- Sliding scales
  - Fixed insulin rate for a glucose value
- Dynamic scales
  - Scale based on last 2 blood glucose levels
Insulin protocol

- Takes into account the rate of change
- Current blood glucose evaluated with prior blood glucose

**INSULIN Infusion Kardex (Adult ICU)**

**PATIENT NAME:**

**Blood Glucose (BG) GOAL:** 80-120 mg/dL in the ICU

1. **Maintenance IV FLUIDS:** ____________ at ____________ mL/hr
   *IV dextrose infusion must be maintained while the patient is on an insulin infusion (even if on Tube Feeds).*

2. **INSULIN infusion rate** ____________ units/hour (Concentration: Regular Insulin 1 unit/mL NS)

3. Start **D$_{50}$W** at 50 mL/hr if TPN or tube feeds are interrupted for longer than 30 minutes and notify MD about change and for further direction/action.

4. Converting or starting subcutaneous (SQ) insulin: The first SQ dose should be administered at least 30 minutes prior to discontinuing insulin infusion.

5. **If current BG is < 60 then**
   - STOP insulin infusion
   - Give 50 mL D50 IV push
   - Notify MD/IO
   - Check BG every 15 minutes and repeat treatment until BG ≥ 80 mg/dL, then check BG q 30 mins until BG ≥ 120 mg/dL.
   - When BG ≥ 120 mg/dL, restart drip at 40% of previous rate (0.40 x previous rate). Round up to the nearest tenth of a unit.

6. **If current BG is 60 to 80 then**
   - STOP insulin infusion
   - Check BG every 30 minutes until BG ≥ 120 mg/dL
   - When BG ≥ 120 mg/dL, restart drip at 50% of previous rate (0.50 x previous rate). Round up to the nearest tenth of a unit.
   - If 2 episodes of BG below 80 in 4 hours, call HO to reevaluate rate

<table>
<thead>
<tr>
<th>C. If current BG is 81 to 120 and previous BG was:</th>
<th>Action Step 1</th>
<th>Check BG in</th>
</tr>
</thead>
<tbody>
<tr>
<td>81 - 100</td>
<td>4 rate by 0.2 unit</td>
<td>1 - 2 hrs</td>
</tr>
<tr>
<td>101 - 120</td>
<td>No change</td>
<td>1 - 2 hrs</td>
</tr>
<tr>
<td>121 - 160</td>
<td>4 rate by 0.5 unit</td>
<td>1 hr</td>
</tr>
<tr>
<td>161 - 200</td>
<td>4 rate by 1 unit</td>
<td>1 hr</td>
</tr>
<tr>
<td>201 - 250</td>
<td>4 rate by 1.5 units</td>
<td>1 hr</td>
</tr>
<tr>
<td>251 - 400</td>
<td>4 rate by 2 units</td>
<td>1 hr</td>
</tr>
<tr>
<td>&gt;400</td>
<td>4 rate by 3 units</td>
<td>1 hr</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D. If current BG is 121 to 160 and previous BG was:</th>
<th>Action Step 1</th>
<th>Check BG in</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤120</td>
<td>1 rate by 0.2 units</td>
<td>1 hr</td>
</tr>
<tr>
<td>121 - 160</td>
<td>1 rate by 0.4 units</td>
<td>1 hr</td>
</tr>
<tr>
<td>161 - 200</td>
<td>No change</td>
<td>1 hr</td>
</tr>
<tr>
<td>201 - 250</td>
<td>4 rate by 0.5 units</td>
<td>1 hr</td>
</tr>
<tr>
<td>251 - 400</td>
<td>4 rate by 1 unit</td>
<td>1 hr</td>
</tr>
<tr>
<td>&gt;400</td>
<td>4 rate by 2 units</td>
<td>1 hr</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E. If current BG is 161 - 200 and compared to previous BG it has</th>
<th>Action Step 1</th>
<th>Check BG in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remained the same or increased</td>
<td>1 rate by 0.3 unit</td>
<td>1 hr</td>
</tr>
<tr>
<td>Decreased by &gt; 1 but &lt; 10 then</td>
<td>1 rate by 0.4 unit</td>
<td>1 hr</td>
</tr>
<tr>
<td>Decreased by ≥ 10 but &lt; 50 then</td>
<td>No change</td>
<td>1 hr</td>
</tr>
<tr>
<td>Decreased by ≥ 50 but &lt; 100 then</td>
<td>4 rate by 0.5 unit</td>
<td>1 hr</td>
</tr>
<tr>
<td>Decreased by ≥ 100</td>
<td>4 rate by 1.5 units</td>
<td>1 hr</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>F. If current BG is &gt; 200 and compared to previous BG it has</th>
<th>Action Step 1</th>
<th>Check BG in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remained the same or increased</td>
<td>1 rate by 1.2 unit</td>
<td>1 hr</td>
</tr>
<tr>
<td>Decreased by &gt; 1 but &lt; 30 then</td>
<td>1 rate by 1 unit</td>
<td>1 hr</td>
</tr>
<tr>
<td>Decreased by ≥ 30 but &lt; 100 then</td>
<td>No change</td>
<td>1 hr</td>
</tr>
<tr>
<td>Decreased by ≥ 100</td>
<td>4 rate by 1 unit</td>
<td>1 hr</td>
</tr>
<tr>
<td>NOT decreased below 200 after 3 adjustments in infusion rate</td>
<td>Call HO</td>
<td>1 hr</td>
</tr>
</tbody>
</table>

**Individualize algorithm for very insulin resistant subjects (insulin > 20 units/hr or G > 300 for more than 4 hr).**

Endocrine service (719-9125) is available for advice (A.7-2005)
Workflow analysis at UCSF

• 33 Patients
• Average BG 136 ± 51 mg/dL
• Took 9.4 hours to reach BG goal
• 19 episodes/ 2265 BG checks of hypoglycemia (BG<60 mg/dL)
  – No clinical harm
• For 1 nurse taking care of 2 pts on protocol, required 2 hours out of a 12 hour nursing shift
Areas to cover

- Cortisol
- Insulin
- Prognostic indices
Endocrine prognostic index

• Can we use endocrine measurements as prognostic indicators to determine mortality
Endocrine tea leaves

• Studies have looked at TSH, T₄, T₃, and cortisol levels

  Rothwell et al, CCM, 23:1; 1995
  Ray et al, Int Care Med, 28, 2002

• Conflicting results from the 2 studies
  – Unclear whether this is more accurate than APACHE II
Results

• Differing times were used for blood sampling
  – What about diurnal values?

• Most were surgical patients
  – Would this apply to medical patients?

• Pts on dopamine or steroids were excluded
  – Were these the sicker patients?
  – What’s the utility of this index if most ICU patients are on these drugs?
# Predictions with Cortisol

<table>
<thead>
<tr>
<th>Cortisol level</th>
<th>Response to CST</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 34 mcg/dL</td>
<td>&gt; 9 mcg/dL</td>
<td>Good</td>
</tr>
<tr>
<td>&lt; 34 mcg/dL</td>
<td>&lt; 9 mcg/dL</td>
<td>Intermediate</td>
</tr>
<tr>
<td>&gt; 34 mcg/dL</td>
<td>&gt; 9 mcg/dL</td>
<td>Intermediate</td>
</tr>
<tr>
<td>&gt; 34 mcg/dL</td>
<td>&lt; 9 mcg/dL</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Annane et al, JAMA, 283; 2000
Predictions with cortisol

- Retrospective analysis of Corticus cohort
- Cortisol levels alone, regardless of cutoff value, were not independent predictors of shock reversal, survival duration, or hospital mortality
Predictions with cortisol
For the Future

• Can the addition of another hormone measurement increase accuracy?
  – Corticotropin stimulation test

• Would this be easier than APACHE or SAPS, which uses clinical measurements and commonly available lab tests?
Conclusion

• **The Good**
  Moderate glucose control

• **The Bad**
  Use of etomidate in patients with sepsis

• **The Unproven**
  Glucocorticoid replacement in patients with septic shock
QUESTIONS?