Endocrine Issues in Critical Illness
Objectives

Be able to identify the following:

- Stress response
- Pathophysiology of stress hyperglycemia
- Immunomodulating properties of glucose and insulin
- Cortisol physiology and biosynthesis
- HPA and the stress response
- Evaluation of HPA in the critically ill
- Adrenal physiology in sepsis
- Steroid replacement in sepsis
The Stress Response

Biologic, physical, or psychologic stressors generally precipitate similar response – “general adaptation syndrome”

The Stress Response

- Activation of the hypothalamic-pituitary (HPA) axis
- Activation of the sympatho-adrenal system
- Activation of subset of vagal and sacral parasympathetic efferents to GUT
The Stress Response

- Activation of HPA axis
  - Cortisol
- Epinephrine
- Norepinephrine
- Glucagon
- Growth hormone
- Prolactin
The Stress Response

- Cardiac output increases
- Respiration increases
- Blood flow directed to brain and skeletal muscle
- Gluconeogenesis and catabolism
  - fuel for brain, heart, muscles
- Endocrine programs of pleasure, growth, and reproduction shut down
Glucocorticoids and the Stress Response

- Increase blood glucose
  - ↑ hepatic gluconeogenesis
  - ↓ adipose tissue glucose uptake
- Lipolysis - FFA release
- Prototeolysis - AA release
- Synthesis of catecholamines
- Synthesis of adrenergic and angiotensin II receptors
- Cardiac contractility
- Vascular tone
Glucagon and Epinephrine Mediated - Gluconeogenesis
Glucagon and Epinephrine Mediated - Glycolysis
Metabolic Consequence of the Stress Response

- Gluconeogenesis
- Gylogenolysis
- Proteolysis
- Lipolysis
- Insulin Resistance

HYPERGLYCEMIA
Critical illness-state characterized by a pathologically prolonged stress response
Acute Stress - Open Cholecystectomy

![Graph showing serum cortisol levels over time after open cholecystectomy surgery.](Image)
The Neuro-endocrine Response to Prolonged Critical Illness

The Neuro-endocrine Response to Prolonged Critical Illness

Nocturnal profile

**Changes in the GH Axis During Critical Illness**

**Acute**
- Inc. pulsatile GH secretion
  - Mobilization fuel
- Low IGF-1, IGFBP-3
  - Dec anabolism
- Dec. GHBP
  - GH resistance
  - Cytokine mediated
  - ? Post-receptor JAK2 kinases

**Chronic**
- Loss of pulsatile GH secretion
- Low IGF-1, IGFBP-3
- Inc GHBP
  - recovery of GH resistance
Stress Hyperglycemia

Definition
- Blood glucose > 200 mg/dl (15 - 20%)
- Blood glucose > 110 mg/dl (75 - 97%)

Etiology
- Increased release of counter-regulatory hormones
  - Increased hepatic gluconeogenesis
- Decreased insulin release
- Insulin resistance
Insulin Mediated Glucose Uptake
Postulated Mechanism of Insulin Resistance in Sepsis
Hyperglycemia and Insulin

Pro-inflammatory

- ↑ROS, NADPH oxidase
  - Oxidative injury
- ↑TNF, IL-8, IL-6
- ↑TF, PAI-1
- CATABOLIC

Anti-inflammatory

- ↓ROS, NADPH oxidase
- ↓ICAM-1, MCP-1
- ↓TNF, IL-6
- ↓TF, PAI-1
- ↑NO synthase
- ANABOLIC
Protein Catabolism and Nitrogen Balance in Acute Renal Failure

Macias WL et al. JPEN 20:56, 1996
Glucose Toxicity
Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients

Hepatocyte

Conventional - 78% abnormal

Intensive - 1% abnormal

Ilse Vanhorebeek, Rita De Vos, Dieter Mesotten, Pieter J Wouters, Christiane De Wolf-Peeters, Greet Van den Berghe

Lancet 2005; 365: 53-59
Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients

Ilse Vanhorebeek, Rita De Vos, Dieter Mesotten, Pieter J Wouters, Christiane De Wolf-Peeters, Greet Van den Berghe

Lancet 2005; 365: 53-59

[Original Articles]

↓ ROS
↓ ICAM-1
↓ MCP-1
↓ PAI-1
Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus
Intensive Insulin Therapy in Critically Ill Patients

![Graph showing in-hospital survival and cumulative hazard (in-hospital death) over days after admission.]

- **Intensive treatment**
  - >150 mg/dl: P = 0.0009
  - 110 - 150 mg/dl: P = 0.026
  - < 110 mg/dl

![Graph with cumulative hazard (in-hospital death) over days after inclusion.]
Intensive Insulin Tx

- More recent studies have not confirmed NEJM findings
  - Keeping BS 80-110 may not have mortality benefit in all patients
  - Keeping BS 80-110 is associated with high incidence of severe hypoglycemia (BS < 50)
### Intensive Insulin Therapy in Critically Ill Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conventional Treatment (N=783)</th>
<th>Intensive Treatment (N=765)</th>
<th>P Value†</th>
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</thead>
<tbody>
<tr>
<td>Administration of insulin — no. (%)</td>
<td>307 (39.2)</td>
<td>755 (98.7)</td>
<td>&lt;0.001</td>
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<tr>
<td>Insulin dose — IU/day‡</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>33</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>17–56</td>
<td>48–100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of insulin use — % of ICU stay</td>
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<tr>
<td>Median</td>
<td>67</td>
<td>100</td>
<td>&lt;0.001</td>
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<tr>
<td>Interquartile range</td>
<td>40–100</td>
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</tr>
<tr>
<td>Morning blood glucose — mg/dl§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>153±33</td>
<td>103±19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients receiving insulin</td>
<td>173±33</td>
<td>103±18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†P values were calculated using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables.
Intensive Insulin Therapy in Critically Ill Patients

200g Dextrose
Intensive Insulin Therapy in Critically Ill Patients

All $P < 0.0001$

- Insulin (IU/h) per (Cal/kg)
- Mean blood glucose (mg/dL)
Intensive Insulin Therapy in Critically Ill Patients

Intensive Insulin Therapy in Critically Ill Patients

Intensive Insulin Therapy in Critically Ill Patients

Regimen 1: 1L 30% sorbitol and 1L 5% glucose
Regimen 2: 1L 50% and 1L 5% glucose
    insulin only BG > 270 mg/dl
Regimen 3: 1L 50% and 1L 5% glucose
    insulin to keep BG 72 - 144 mg/dl
Relative Influence of Glucose and Insulin on Peripheral Amino Acid Metabolism in Severely Burned Patients

Dennis C. Gore, MD; Steven E. Wolf, MD; David N. Herndon, MD; and Robert R. Wolfe, PhD

<table>
<thead>
<tr>
<th>Amino Acid net balance across the leg (nmol/min/100 ml leg vol)</th>
<th>Fasting</th>
<th>Glucose</th>
<th>Insulin</th>
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</thead>
<tbody>
<tr>
<td>Asp</td>
<td>-3.3 ± 0.6</td>
<td>-14.0 ± 6.1</td>
<td>-0.7 ± 0.5</td>
</tr>
<tr>
<td>Glu</td>
<td>-6.3 ± 1.1</td>
<td>-42.1 ± 3.4*</td>
<td>-4.7 ± 6.0</td>
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<tr>
<td>Asn</td>
<td>-0.8 ± 0.1</td>
<td>-6.6 ± 1.7</td>
<td>-0.7 ± 1.1</td>
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<tr>
<td>Ser</td>
<td>-3.0 ± 11.1</td>
<td>-10.0 ± 29.7</td>
<td>-7.7 ± 0.9</td>
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<tr>
<td>Gln</td>
<td>-64.9 ± 13.4</td>
<td>-219.9 ± 19.7*</td>
<td>-23.9 ± 11.0</td>
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<tr>
<td>His</td>
<td>-9.2 ± 0.7</td>
<td>-27.1 ± 2.9</td>
<td>18.0 ± 3.4</td>
</tr>
<tr>
<td>Gly</td>
<td>-6.5 ± 1.1</td>
<td>-119.1 ± 31.1*</td>
<td>-14.3 ± 16.0</td>
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<tr>
<td>Thr</td>
<td>-29.6 ± 8.1</td>
<td>-60.3 ± 12.1</td>
<td>-12.1 ± 3.4</td>
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<tr>
<td>Arg</td>
<td>-109 ± 27.7</td>
<td>-111.2 ± 21.1</td>
<td>34.7 ± 17.0</td>
</tr>
<tr>
<td>Ala</td>
<td>-116.7 ± 14.6</td>
<td>-167.5 ± 18.7*</td>
<td>-92.1 ± 11.0</td>
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<td>Tyr</td>
<td>-3.8 ± 0.6</td>
<td>-30.5 ± 7.9</td>
<td>0.2 ± 3.4</td>
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<tr>
<td>Val</td>
<td>-17.1 ± 4.1</td>
<td>-35.9 ± 8.7</td>
<td>-7.9 ± 5.1</td>
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<tr>
<td>Met</td>
<td>-19.6 ± 9.1</td>
<td>-21.9 ± 7.3</td>
<td>-9.6 ± 3.7</td>
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<tr>
<td>Trp</td>
<td>-2.7 ± 0.6</td>
<td>-46 ± 14.4*</td>
<td>1.7 ± 1.8</td>
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<tr>
<td>Phe</td>
<td>-15.5 ± 0.9</td>
<td>-21.8 ± 1.1</td>
<td>4.7 ± 1.1</td>
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<tr>
<td>Ile</td>
<td>-17.7 ± 1.9</td>
<td>-16.2 ± 2.1</td>
<td>-4.4 ± 0.7</td>
</tr>
<tr>
<td>Leu</td>
<td>-20.4 ± 8.1</td>
<td>-36.4 ± 7.4</td>
<td>-1.2 ± 0.8</td>
</tr>
<tr>
<td>Lys</td>
<td>-62.3 ± 7.9</td>
<td>-124.0 ± 9.1*</td>
<td>-44.5 ± 3.3</td>
</tr>
<tr>
<td>Cumulative</td>
<td>-723.6 ± 71.6</td>
<td>-1330.7 ± 162.0**</td>
<td>-194.5 ± 25.0</td>
</tr>
</tbody>
</table>

Mean ± SEM.
Anabolic Effects of Insulin and Amino Acids in Promoting Nitrogen Accretion in Postoperative Patients

R. Valarini,* M. F. Sousa,* R. Kalil,* N. N. Abumrad;† and M. C. Riella*

From the *Departments of Medicine and Surgery, Evangelic School of Medicine, Curitiba, Brazil, and the †Department of Surgery, The State University of New York, Stony Brook

Nitrogen grams

Hyperglycemia: TEN versus TPN

- Trauma meta-analysis
- TEN (n = 92) versus TPN (n = 102)
- Similar ATI, ISS, BEE, organ injuries
- Goal: 0.2 - 0.25 g N/kg/d

Physiologic Effects of Enteral and Parenteral Feeding on Pancreaticobiliary Secretion in Humans

Increased Mortality Associated with Growth Hormone Treatment in Critically Ill Adults

Jukka Takala, M.D., Ph.D., Esko Ruokonen, M.D., Ph.D., Nigel R. Webster, M.D., Michael S. Nielsen, M.D., Durk F. Zandstra, M.D., Guy Vandevenckx, M.D., and Charles J. Hinds, M.D.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>GH</th>
<th>p</th>
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<tbody>
<tr>
<td>Finnish Study</td>
<td>20%</td>
<td>39%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(n = 242)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Multi-national study</td>
<td>18%</td>
<td>44%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(n = 280)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Glucose greater in GH group, p < 0.001
Nitrogen retention greater in GH group, p = 0.002
Glucose Control in the ICU

THE GOOD

- Glycemic control
  - BS < 110-150
  - Insulin?
- Early enteral nutrition
- Slowly absorbed CHO
- Permissive underfeeding
- Omega 3 FA

THE BAD

- High glucose load
- High caloric intake
- Poor glycemic control
- Rapidly absorbed CHO
- GH
- TPN
- Low omega 3FA
Adrenal Insufficiency in the Critically Ill
Cortisol
The Hypothalamic-Pituitary-Adrenal Axis

- **Hypothalamus**
  - STRESS
  - CRH
- **Pituitary**
  - ACTH
  - Cortisol
- **Adrenal**
Steroid Hormone Receptor Trafficking Through the Nuclear Compartment

HSP90
FKBP51
FKBP52
Dynein
Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells

845 genes  1125 genes
Synthesis of Cortisol

80% exogenous
20% endogenous
HDL as Substrate Cholesterol for Steroidogenesis by Bovine Adrenal Cells

Cortisol production (ng/10^5 cells)

Incubation time (min)

Scavenger Receptor, Type B, Class 1
Cortisol Synthesis

ACTH → HDL Receptor (SR-B1) → Stromal receptor, (Junction 3, type 1)

ACTH → Cholesterol → Steroidogenic acute regulatory protein (STAR)

ACTH → Prenololone → CYP11A → CYP11B1

CYP17 → 17α-hydroxylase → 11-Deoxycortisol

CYP21 → 3β-HSD isomerase → 17αH-Progesterone
The Neuro-endocrine Response to Prolonged Critical Illness

Free Serum Cortisol During the Post-op Period Determined by Mass Spectrometry

“Normal” Stress Response

- ACTH > 40 pg/dl
- Cortisol level > 20 ug/dl
- CBG ↓
- Free cortisol ↑↑
- Glucocorticoid receptor ↑
- Androgen synthesis ↓
- Aldosterone synthesis ↓
Cortisol and the Stress Response

Fight and flight response
- Glucose – fuel
- Hemodynamic reserve

Suppress activated defense mechanisms
- Prevent tissue damage
- Prevent excessive inflammation
Adrenalectomy and Survival Following Hemorrhage

“Gold Standard” - Stress Cortisol

When stress is not adequate:

- Provocative testing
  - Insulin hypoglycemia, metyrapone test
- CRH stimulation test
- ACTH (corticotropin) stimulation test
  - Standard - 250 ug
  - Low dose - 1 ug
Standard ACTH Test

- Baseline cortisol
- 250 ug cosyntropin
- 1 hour level
  - 1 hour < 18 ug/dl (AI)
  - ≥ 9 ug/dl - “Occult AI”
  - Annane - “Non responder”
Problems with Classic ACTH Test

- Bypasses the hypothalamus and pituitary
  - unphysiological compared to endogenous stressor

- Produces supra-physiological levels of ACTH
  - serum levels \(1000 \times\) maximal normal stress levels

- Cutoff of 18 mcg/dl based on response to ACTH in nonstressed patients

- Severely stressed patients may not increase levels further.

- CORTICUS Trial suggests ACTH stimulation does not have predictive value in critical illness
Problems with Classic ACTH Test

~ 50% of healthy volunteers and stressed patients without evidence of HPA disease will have a cortisol < 9ug/dl.
Hypothalamic-pituitary-adrenal axis dysfunction in critically ill patients with traumatic brain injury: Incidence, pathophysiology, and relationship to vasopressor dependence and peripheral interleukin-6 levels*

Dimopoulou, Ioanna MD; Tsagarakis, Stylianos MD, PhD; Kouyialis, Andreas T. MD; Roussou, Paraskevi MD; Assithianakis, Georgios MD; Christoforaki, Marietta MD; Ilias, Ioannis MD; Sakas, Damianos E. MD; Thalassinos, Nikolaos MD; Roussos, Charis MD, PhD

RESULTS

Endocrine Evaluation in Healthy Volunteers

Baseline and stimulated cortisol levels after LDST were 15.5 ± 4.2 μg/dL and 23.3 ± 2.9 μg/dL, respectively. The median increment in cortisol was 7.3 μg/dL. Stimulated cortisol expressed as fifth percentile was 18.4 μg/dL.
Adrenocortical Dysfunction Following Etomidate Induction in Emergency Department Patients

Christina L. Schenarts, MD, John H. Burton, MD and Richard R. Riker, MD
Low-dose Corticotropin Test

J Clin End Metab. 1999;84:3648.
Low-Dose Adrenocorticotropic Test Reveals Impaired Adrenal Function in Patients Taking Inhaled Corticosteroids

Diagnosis of HPA Failure

- Clinical
- High-dose (250 ug) cosyntropin stimulation test
- Low-dose (1ug) cosyntropin stimulation test
- Urinary cortisol (free)
- Random “stress” cortisol (total s-cortisol)
- Salivary cortisol (free)
- Free cortisol index
- Free cortisol
- Intra-nuclear cortisol
- Gene product
Adrenal Insufficiency in the Critically Ill – Clinical Presentation

- Adrenergic receptors
- Catecholamine
- Increased proinflammatory mediators
- NF-KB
- Hypotension
- Confusion
- Fever

Society of Critical Care Medicine
The Intensive Care Professionals

Resident ICU Course
Clinical Diagnosis of HPA Failure

- Hypotension
- Hemodynamic instability
- Fever
- Unexplained confusion
- Eosinophilia
- Hypoglycemia
Reversible Adrenal Insufficiency of Sepsis
Sepsis and the HPA Axis

IL-1
IL-6

CRH

ACTH

TNF
Corticostatin
++ IL-1
Endotoxin
TGF-beta
ACTH-variants
Other??

Decreased glucocorticoid receptor synthesis and affinity
TNF and Cortisol Production

Binding and Internalization of Lipopolysaccharide by Cla-1, a Human Orthologue of Rodent Scavenger Receptor B1*

Received for publication, October 29, 2002, and in revised form, March 13, 2003
Published, JBC Papers in Press, March 21, 2003, DOI 10.1074/jbc.M211032200

Tatyana G. Vishnyakova§, Alexander V. Bocharov§§, Irina N. Baranova§, Zhigang Chen§, Alan T. Remaley§§, Gyorgy Csako§, Thomas L. Eggerman§§, and Amy P. Patterson‡

From the §NHLBI, National Institutes of Health, Bethesda, Maryland 20892, the §§Department of Laboratory Medicine, W. G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland 20892, and the ¶Division of Diabetes, Endocrinology and Metabolic Diseases, NIDDK, National Institutes of Health, Bethesda, Maryland 20892
Lipoprotein metabolism in patients with severe sepsis

van Leeuwen, Henk J. MD; Heezius, Eric C. J. M.; Dallinga, Geesje M. PhD; van Strijp, Jos A. G. PhD; Verhoef, Jan MD, PhD; van Kessel, Kok P. M. PhD
Relationship of hypolipidemia to cytokine concentrations and outcomes in critically ill surgical patients

Gordon, Bruce R. MD; Parker, Thomas S. PhD; Levine, Daniel M. PhD; Saal, Stuart D. MD; Wang, John C. L. MD, PhD; Sloan, Betty-Jane MA; Barie, Philip S. MD, FACS, FCCM; Rubin, Albert L. MD
Cytokines Decrease Apolipoprotein Accumulation in Medium From Hep G2 Cells

Walter H. Ettinger, Vivek K. Varma, Mary Sorci-Thomas, John S. Parks, Rita C. Sigmon, Thuy K. Smith, Roy B. Verderery

### HDL-cholesterol level and cortisol response to synacthen in critically ill patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Responders</th>
<th>Non-responders</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>2.0 (1.1–4.2)</td>
<td>2.2 (1.1–4.2)</td>
<td>1.9 (1.1–3.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>0.49 (0.1–1.6)</td>
<td>0.69 (0.16–1.6)</td>
<td>0.33 (0.1–1.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>0.82 (0.0–2.4)</td>
<td>0.81 (0.3–2.4)</td>
<td>0.86 (0.0–1.6)</td>
<td>0.78</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.1 (0.4–7.3)</td>
<td>1.0 (0.4–2.2)</td>
<td>1.2 (0.53–7.3)</td>
<td>0.11</td>
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<tr>
<td>Basal cortisol (μmol/l)</td>
<td>0.55 (0.04–1.68)</td>
<td>0.49 (0.39–0.95)</td>
<td>0.57 (0.05–1.6)</td>
<td>0.41</td>
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<tr>
<td>Cortisol 30 min (μmol/l)</td>
<td>0.75 (0.05–1.75)</td>
<td>0.79 (0.26–1.75)</td>
<td>0.68 (0.05–1.75)</td>
<td>0.32</td>
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<tr>
<td>Cortisol 60 min (μmol/l)</td>
<td>0.78 (0.05–1.75)</td>
<td>0.82 (0.30–1.75)</td>
<td>0.68 (0.05–1.75)</td>
<td>0.12</td>
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<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>Sign</th>
<th>OR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>HDL</td>
<td>−3.87</td>
<td>1.92</td>
<td>4.0</td>
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<td>0.020</td>
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<td>TC</td>
<td>1.62</td>
<td>1.31</td>
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<td>1</td>
<td>0.21</td>
<td>5.09</td>
<td>0.38–67</td>
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<td>LDL</td>
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<td>1.58</td>
<td>0.48</td>
<td>1</td>
<td>0.48</td>
<td>0.33</td>
<td>0.015–7.4</td>
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<td>SOFA</td>
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<td>0.14</td>
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<td>1</td>
<td>0.99</td>
<td>0.99</td>
<td>0.75–1.32</td>
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<td>Const</td>
<td>−0.74</td>
<td>1.77</td>
<td>0.17</td>
<td>1</td>
<td>0.67</td>
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</tr>
</tbody>
</table>
ACTH Response During Septic Shock and after Recovery (in patients with HPA failure)

13 of 20 patients BL < 25 mg/dl

Adrenal insufficiency during septic shock

Paul E. Marik, MD, FCCM; Gary P. Zaloga, MD, FCCM

Objectives: To determine whether a baseline (random) cortisol concentration <25 μg/dL in patients with septic shock was a better discriminator of adrenal insufficiency than the standard (250 μg) and the low-dose (1 μg) corticotropin stimulation tests as assessed by the hemodynamic response to steroid replacement.

Setting: Intensive care unit.

Patients: Fifty-nine patients with septic shock. Their mean age was 57 ± 16.7 yrs; 29 were male.

Interventions: A baseline cortisol concentration was obtained. Patients then received an intravenous injection of 1 μg of corticotropin (low-dose test) followed 60 mins later by an injection of 249 μg of corticotropin (high-dose test). Cortisol concentrations were obtained 30 and 60 mins after low- and high-dose corticotropin. All patients were administered hydrocortisone (100 mg every 8 hrs) for the first 24 hrs while awaiting results of cortisol assessment. Patients were considered steroid responsive if the pressor agent could be discontinued within 24 hrs of the first dose of hydrocortisone.

Measurements and Main Results: Forty-seven percent of patients died. Twenty-two percent of patients met the diagnostic criteria of adrenal insufficiency by the low-dose test and 8% by the high-dose test. However, 61% of patients met the criteria of adrenal insufficiency when we used a baseline cortisol concentration of <25 μg/dL. Twenty-two patients (37%) were steroid responsive; the baseline serum cortisol was 14.1 ± 5.2 μg/dL in the steroid-responsive patients compared with 33.3 ± 16 μg/dL in the steroid-nonresponsive patients (p < .0001). Ninety-five percent of steroid-responsive patients had a baseline cortisol concentration <25 μg/dL. Fifty-four percent of steroid responders had a diagnostic low-dose test and 22% a diagnostic high-dose test. Receiver operating characteristic curve analysis revealed that a stress cortisol concentration of 29.7 μg/dL was the most accurate diagnostic threshold for determination of the hemodynamic response to glucocorticoid therapy.

Conclusions: Adrenal insufficiency is common in patients with septic shock, the incidence depending largely on the diagnostic test and criteria used to make the diagnosis. There is clearly no absolute serum cortisol concentration that distinguishes an adequate from an insufficient adrenal response. However, we believe that a random cortisol concentration of <25 μg/dL is a useful diagnostic threshold for the diagnosis of adrenal insufficiency. (Crit Care Med 2002; 31:xxxxxxx)

Key Words: sepsis; shock; adrenal insufficiency; cortisol; corticotropin; hypothalamic-pituitary-adrenal axis; endocrine; glucocorticoids
Hydrocortisone Infusion in Patients with Severe CAP: A RCT

<table>
<thead>
<tr>
<th>n = 46</th>
<th>Placebo</th>
<th>Hydrocortisone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dev. MODS</td>
<td>16 (70%)</td>
<td>8 (35%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration ventilation</td>
<td>10</td>
<td>4</td>
<td>0.007</td>
</tr>
<tr>
<td>Hosp LOS</td>
<td>21</td>
<td>13</td>
<td>0.03</td>
</tr>
<tr>
<td>Hosp Mortality</td>
<td>7 (30%)</td>
<td>0</td>
<td>0.009</td>
</tr>
</tbody>
</table>

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

[Caring for the Critically Ill Patient]

Annane, Djillali MD, PhD; Sébille, Véronique PhD; Charpentier, Claire MD; Bollaert, Pierre-Edouard MD, PhD; François, Bruno MD; Korach, Jean-Michel MD; Capellier, Gilles MD, PhD; Cohen, Yves MD, PhD; Azoulay, Elie MD; Troché, Gilles MD; Chaumet-Riffaut, Philippe MD; Bellissant, Eric MD, PhD
Study Description

Design

- Randomized, double-blind, placebo-controlled trial
- 19 ICUs France, 1995 - 1999

Population – Septic Shock

- Focus of infection + HR >90/min + fever/hypothermia
- SBP < 90 mm Hg for 1 hour despite fluid /pressors
- Randomization within 8 hours shock

Treatment Arms

- Randomization to hydrocortisone 50mg IV q 6 + 50 ug fludrocortisone PO qd or matching placebo
Study Description

**Adrenal assessment**
- **250 ug corticotropin test**
- **Responders**
  - increase cortisol $> 9$ ug/dl
- **Non-responders (occult adrenal insufficiency)**
  - increase cortisol $< 9$ ug/dl

**End-points**
- **28-day mortality**
- **Time to vasopressor withdrawal**
Hydrocortisone Increases Survival in Septic Shock

- 30% relative risk reduction (RRR) of death
- Survival (%): Treatment vs Placebo
- n = 299
- p = 0.0096
- Time (days) from 0 to 28
CORTICUS

- Larger, multinational, European
- RCT design
- Differences with Annane
  - Did not include fludrocortisone
  - Enrolled patients up to 3 days following onset of sepsis
  - Steroids dosed for 11 days with 6 day taper

NEJM 2008; 358 : 111-124
ACTH stimulation is not predictive of response to exogenous steroid.
Exogenous steroid administration has a vasopressor sparing effect.
Exogenous steroid administration does not have mortality benefit.
Steroid group had higher incidence of infection and recurrent severe sepsis/shock.

NEJM 2008; 358 : 111-124
Immunologic and Hemodynamic Effects of "Low-Dose" Hydrocortisone in Septic Shock

A Double-Blind, Randomized, Placebo-controlled, Crossover Study

Didier Keh, Thomas Boehnke, Steffen Weber-Cartens, Christina Schulz, Olaf Ahlers, Sven Bercker, Hans-Dieter Volk, Wolf-Dietrich Doecke, Konrad J. Falke and Herwig Gerlach
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Conclusions

- Adrenal insufficiency (AI) common in ICU patients, especially those with sepsis.

- Decreased synthesis of cortisol and release of ATCH mediated by cytokines, endotoxin, low HDL, etc.

- Diagnosis of AI controversial

- Role for treatment with replacement doses of hydrocortisone (50 - 100 mg q8) remains uncertain.