Glucose Metabolism in Sepsis

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Hyperglycemia & Sepsis

- Adaptive response
  - Maintains intravascular volume
  - Increases energy delivery to vital organs

- For some processes in critical care, supra physiologic responses are associated with improved survival......
Many studies have shown worse morbidity / mortality for adults with hyperglycemia

- Stroke (Stroke 2001; 32: 2425-32)
- Burns (J Trauma 2001; 51: 540-4)
- Trauma (J Trauma 2004; 56: 1059-62)
- MI  (Lancet 2000; 355: 773-8)
Hyperglycemia & Worse Outcome Critically Children

- TBI (Cochran A Trauma 2003;55:1035-8)
Trials to Improve Nitrogen Balance: GH

- Septic adults
  - rh GH 0.1 mg/kg/day for 8 days improved nitrogen balance (Ann Surg 1992; 216:648)
  - Associated with ↑ insulin resistance

- Critically ill adults: 2 RCTs
  - rh GH 5.3 mg or 8 mg daily (based on weight)
  - Associated with ↑ insulin resistance & mortality
  - ↑ mortality vs. placebo (39% vs. 20% and 44% vs. 18%) (N Engl J Med 1999; 341: 785-792)
Randomized Trial: Hyperglycemia treated in SICU

- Tight Glucose Control (80-11 vs 180-210 mg/dL)
  - ↓ sepsis in ICU (7.8% vs. 4.8%)
  - ↓ dialysis (8.2% vs. 4.8%)
  - ↓ ventilation > 14 days (11.9% vs. 7.5%)
  - ↓ polyneuropathy (51.9% vs. 28.7%)
  - ↓ mortality (8.0% vs. 4.6%)
Adult MICU Trial – Less Dramatic


- ↓ new kidney disease
  - 8.9% vs. 5.9%

- ↓ time of mechanical ventilation
  - HR 1.21; 95% CI 1.02-1.44

- ↓ mortality for those >3 day stay
  - 52.5% VS 43.0
Stress Physiology \(\rightarrow\) Hyperglycemia

- Trials in 1980’s with healthy subjects replicated critical illness hyperglycemia
  - Gave glucose counter regulatory hormones
  - ↑ Glucose production 100%
  - ↑ Blood Glucose 60-80%
- Hyperglycemia due to production increases primarily rather than ↓ extraction
Stress Physiology, Sepsis and Treatment

↑ Glucagon
↑ Catecholamines
↑ GH & Cortisol

↑ Insulin
↑ Insulin Resistance

↑ Cytokines (TNFα, IL-1, IL-6)

Administration of Dextrose, Steroids, Catecholamines

↑↑↑ [glu]
Catecholamines

- **Epinephrine**
  - Gluconeogenesis
  - Glycogenolysis
  - Direct suppression of insulin secretion
  - Skeletal muscle & liver
  - Lipolysis $\rightarrow$ ↑ FFA

- **Norepinephrine**
  - Gluconeogenesis
  - Less effect than epinephrine
  - Glycogenolysis
  - Very weak in liver
  - Lipolysis $\rightarrow$ ↑ FFA
Glucocorticoids

- Diurnal variation lost with stress
- ↑ CRH & ACTH
- Cytokines modulate cortisol production & receptor number & affinity
- Cortisol binding protein ↓ due to elastase activity → ↑ free cortisol
- However, response is variable in septic shock
Growth Hormone

- Normal pulsatile secretion
- Stress $\uparrow$ peak & pulse frequency
- Tissue expression $\rightarrow$ $\downarrow$ IGF-1, IGFBP-3, & its Acid Labile Subunit
- Usual state - peripheral resistance
Glucose Transporters

- Lipid bilayers
- Transport systems identified
- Sodium linked transporters
  - intestine & kidney
  - against concentration gradient
- GLUT transporters
  - facilitated diffusion
  - down concentration gradients
Glucose Transporters GLUT1-5

- **GLUT1**
  - Concentrated in brain, RBC, endothelial cells

- **GLUT2**
  - Kidneys, liver, small bowel, pancreas

- **GLUT3**
  - Neurons, placenta

- **GLUT4** - *insulin responsive glucose transporter*
  - Skeletal muscle, cardiac muscle, adipose tissue

- **GLUT5**
  - Fructose transporter, low affinity for glucose
Stress-Induced Changes in Glucose Homeostasis

- Impaired uptake - GLUT4 and insulin receptors
  - Immobilization
  - Glucocorticoids, GH, catecholamines
  - LPS, TNF-α
  - Palmitate (FFA)
  - GH ↓ insulin receptors

- Increased uptake - liver, brain, endothelial cells
  - Up regulation of GLUT1 & 3 (non insulin dependent transport)

- Increased hepatic glucose production
Clin Chest Med 1996; 17:249
Lactate Metabolism & Production

- Normally lactate dehydrogenase maintains lactate/pyruvate 20:1
  - ↓ sepsis can decrease 1:1 due to both delayed clearance and decrease enzyme activity
  - However, septic adults showed ↑ lactate due to ↑ glucose production rather than PDH inhibition (Ann Surg 1996; 224: 97-104)


- WBC metabolism largely anaerobic
Lactic Acidosis & Sepsis

**HYPERLACTATEMIA**

- **↑ lactate production**
  - Anaerobic
    - Tissue hypoxia
    - Increased WBC metabolism
  - Aerobic
    - Endogenous production
    - Inflammation mediated:
      - Accelerated glycolysis
      - Inhibition of pyruvate dehydrogenase

- **↓ lactate clearance**
  - Impaired liver function
  - Decreased liver blood flow
Hyperglycemia - Reactive Oxygen Species

- ↑ [glu] → ↑ mitochondrial resting potential → generation of ROS
- [glu] also involved in NADPH pathway in pentose phosphate pathway
ROS

☐ Concentrated in
  ■ Phagocytic cells
    □ macrophages, Kupffer cells & PMNs
  ■ Epithelial cells
    □ enterocytes, hepatocytes, alveolar & renal tubular cells

☐ Leads to mitochondrial damage
Intracellular hyperglycemia transported by GLUT1-3 (Brain, gut, liver, kidneys, immune cells) exacerbate mitochondrial superoxide formation.

- Superoxide + NO $\rightarrow$ ↑ peroxynitrite
- Peroxinitrites $\rightarrow$ tyrosine nitration of proteins to alter function
- Mitochondrial damage likely leads to MSOF
Lipid & Muscle Metabolism during Stress

Diagram:
- SKELETAL MUSCLE
  - Proteolysis
- PERIPHERAL TISSUES
  - Glycolysis
  - Lactate
- LIVER
  - Gluconeogenic substrates
  - Glucose
  - Glycogen
  - Systemic glucose
- ADIPOCYTE
  - Lipolysis
  - Counterregulatory hormones
  - Insulin
  - Alanine
  - Glycero
Lipid metabolism

- ↑ FFA
- ↑ TG
- ↓ HDL, LDL
- Impaired intracellular transport of long chain FFA esters
Effects of Increased Intracellular [Long Chain FFA Esters]

$\uparrow$ [long-chain fatty acid esters]

- PDH
  - Uncouples oxidative phosphorylation
  - $\uparrow$ [lactate]

- NADH pathway
  - $\downarrow$ gluconeogenesis

- $\Delta$ ketogenesis
  - $\uparrow$ $\beta$-hydroxybuterate

- ROS
Muscle Catabolism

- Muscle catabolism $\rightarrow$ alanine $\rightarrow$ glutamine
  - Muscle [glutamine] $\downarrow$ 80-90% with severe stress
- $\uparrow$ gluconeogenesis
Immune Function & Hyperglycemia

- ↑ CRP
- Glycosylates immunoglobulins
- ↓ Granulocyte function
  - Impaired adhesion, chemotaxis, respiratory burst, superoxide, intracellular killing
- ↓ Complement function
  - Micro organism attachment impaired
  - Impaired opsonization
Other effects of Hyperglycemia

- Vascular endothelial dysfunction $\rightarrow$ ↑ NO
- Hypercoagulable state
  - Platelet activation, inhibition of fibrinolytic system, altered clotting factors
Hyperglycemia Treatment

- Difficult to distinguish effects of:
  - Insulin dependent [glu]
  - Decreased [gluc]
  - Finney et al (JAMA 2003; 290: 2041-2047) analysis suggested [gluc] control, rather than increased insulin dosing, associated with survival
Insulin therapy for stress hyperglycemia

- **Muscle**
  - ↑ mRNA for GLUT4 in muscle
  - ↑ mRNA for hexokinase II
  - Rate limiting enzyme of intracellular insulin stimulated glucose metabolism

- **Liver**
  - No effect on expression of phosphoenolpyruvate carboxykinase
  - Rate limiting enzyme for glycogen synthesis
  - Preserves mitochondrial ultrastructure
  - Restores lipid profile
  - ↓ TG, ↑ HDL & LDL

- **Immune System**
  - ↓ CRP
Glucose & Pediatric Septic Shock

- Branco et al. (Pediatric Crit Care Med 2005; 6: 470-472)
- Prospective cohort study of fluid-refractory pediatric septic shock
- N=57
- Peak mean [glu] 214 mg/dL (+/-98)
- Overall mortality: 49%
- [Glu] associated with death
  - Mean 262 vs. 168 mg/dL
- Cutoff of 178 mg/dL predictive of mortality
  - 28% vs. 71%
Insulin levels and meningococcal sepsis

- Van Waardenburg et al (J Clin Endocrinol Metab 2006; 91: 3916-3921)
  - Prospective cohort study 16 children with meningococcal sepsis (6 without shock-treated with only fluid boluses)
  - Measured blood glucose for 3 days, hormones that regulate [glu], cytokines
Van Waardenburg Study

- Peak [glu] ↑ in shock patients
- Mean [glu] ↑ on day 2 & 3 in shock patients
- Plasma [insulin] ↓ in shock patients
  - 7.2 vs. 19 mU/L (both within normal range)
- Plasma insulin/[gluc] ↓ in shock patients
  - 1.1 vs. 3.4
- Cortisol, GH, glucagon, IGF-1 normal range & not different by group
- TNF & CRP ↑ in shock patients
Glucose metabolism: Pediatric & Adult Septic Shock

- Insufficient insulin response to hyperglycemia in pediatric shock
  - Insulin deficiency differs from adult patients with insulin resistance
- Higher cytokine levels may have a role in insulin suppression
## Sepsis in Children in 1995 (US)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Annual incidence</strong>: 0.56/1000</td>
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<tr>
<td><strong>Highest in infants</strong>: 5.2/1000</td>
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<td><strong>VLBW or other underlying disease</strong></td>
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<td><strong>Respiratory infection &amp; bacteremia most common</strong></td>
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<td><strong>Mortality</strong>: 10.3%</td>
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<td>■ 4400 deaths per year</td>
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Conclusions

- Glucose regulation is complicated
- Children may differ by age with less insulin resistance compared to adults
  - Developmental changes may be important as infants are high risk group
- Mortality lower - more difficult to show benefit of insulin or other therapies