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……

Hyperglycemia & Critical Illness

- Many studies have shown worse morbidity / mortality for adults with hyperglycemia
  - TBI (Neurosurgery 2000;46: 335-42, J Trauma 2005;58: 47-50)
  - 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

- Drowning (Christensen DW *Pediatrics.* 1997; 99:715-721 and Graf WD *Ann Emerg Med.* 1995; 26:312-319)
- TBI (Cochran A *Trauma* 2003;55:1035-8)
- General ICU (Wintergerst KA *J Pediatr* 2006; 118; 173-179, Srinivasan V *Pediatr Crit Care Med* 2004:5: 329-335, Faustino EV *J Pediatr* 2005; 146:30-34)

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

- Van Den Berghe *et al* (N Engl J Med 2001; 345: 1359-67)
- 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

- Van den Berghe *et al* (N Engl J Med 2006; 354; 449-461)
- ↓ 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 → 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
    - skeletal muscle & liver
  - Lipolysis → ↑ FFA
  - Direct suppression of insulin secretion
- Norepinephrine
  - Gluconeogenesis
    - less effect than epinephrine
  - Glycogenolysis
    - very weak in liver
  - Lipolysis → ↑ 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

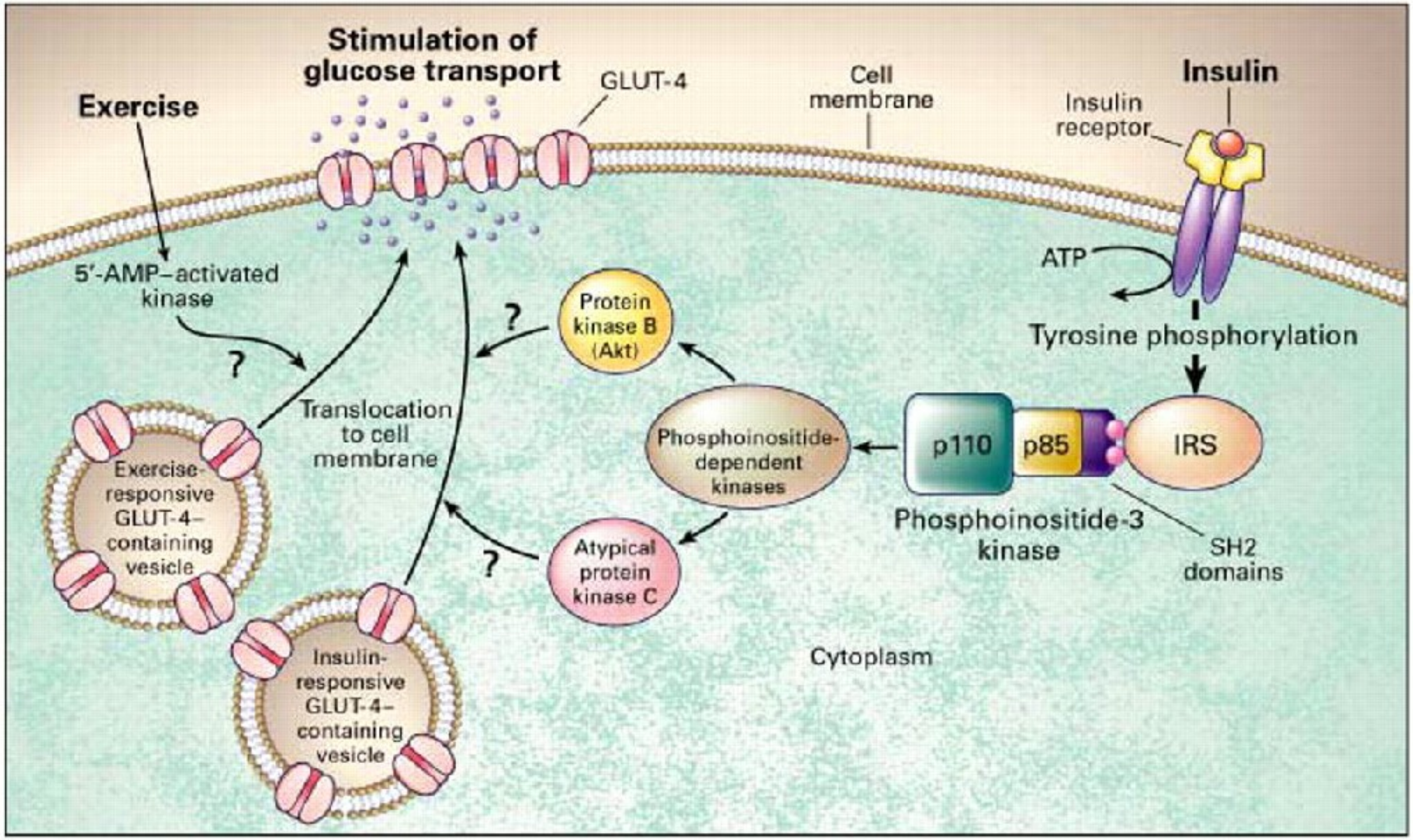
- Normal pulsatile secretion
- Stress ↑ peak & pulse frequency
- Tissue expression → ↓ IGF-1, IGFBP-3, & its Acid Labile Subunit
- Usual state - peripheral resistance

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

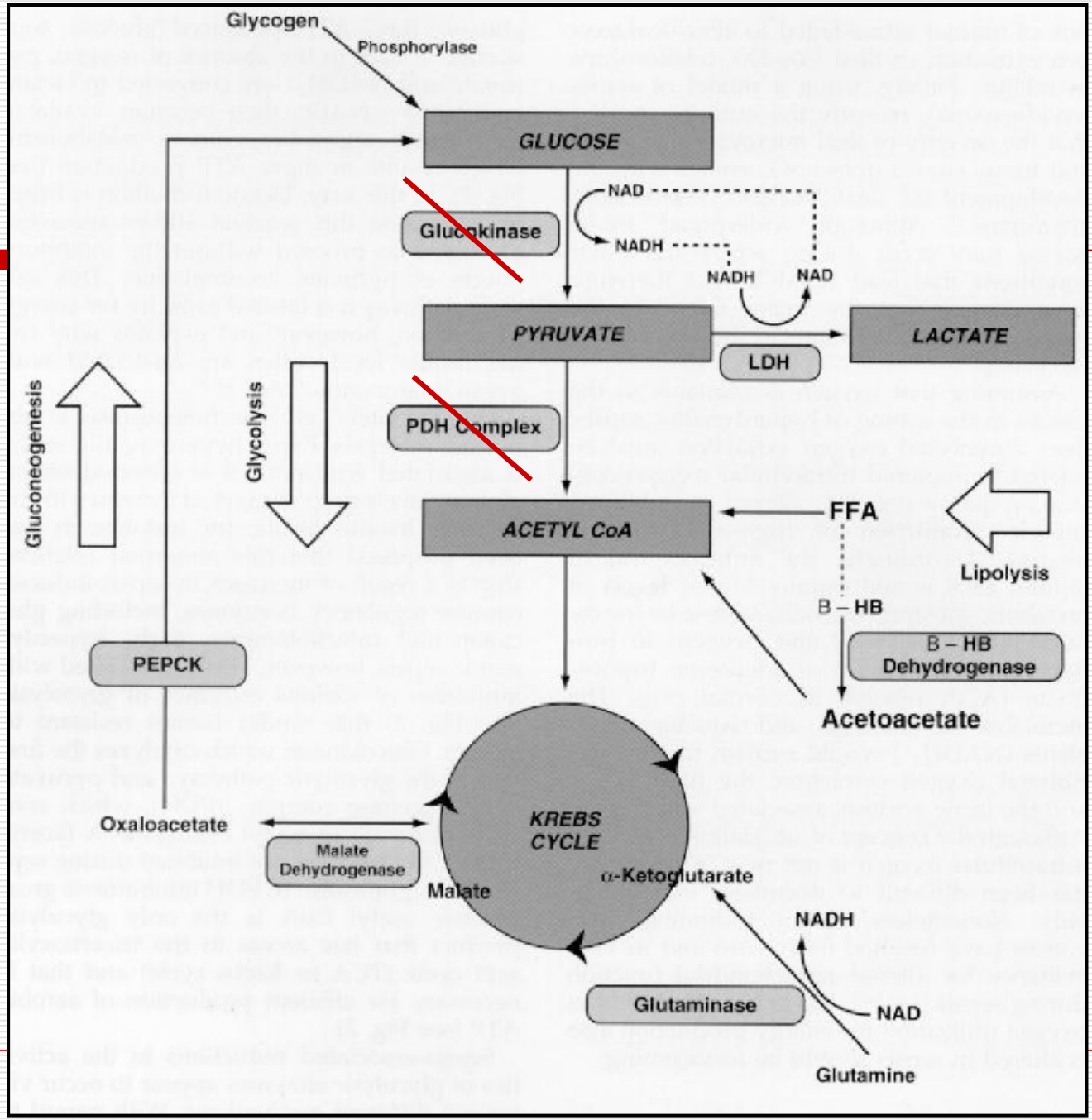
- GLUT1
  - Concentrated in brain, RBC, endothelial cells
- GLUT2
  - Kidneys, liver, small bowel, pancreas
- GLUT3
  - Neurons, placenta
- GLUT4 -**insulin responsive glucose transporter**
  - Skeletal muscle, cardiac muscle, adipose tissue
- GLUT5
  - Fructose transporter, low affinity for glucose



N Engl J Med 1991; 342:248

Stress-Induced Changes in Glucose Homeostasis

- Impaired uptake-GLUT4 and insulin receptors
  - Immobilization
  - Glucocorticoids, GH, catecholamines
  - LPS, TNF-α
  - Palmitate (FFA)
  - GH $\downarrow$ insulin receptors
- Increased uptake - liver, brain, endothelial cells
  - Up regulation of GLUT1 & 3 (non insulin dependent transport)
- Increased hepatic glucose production

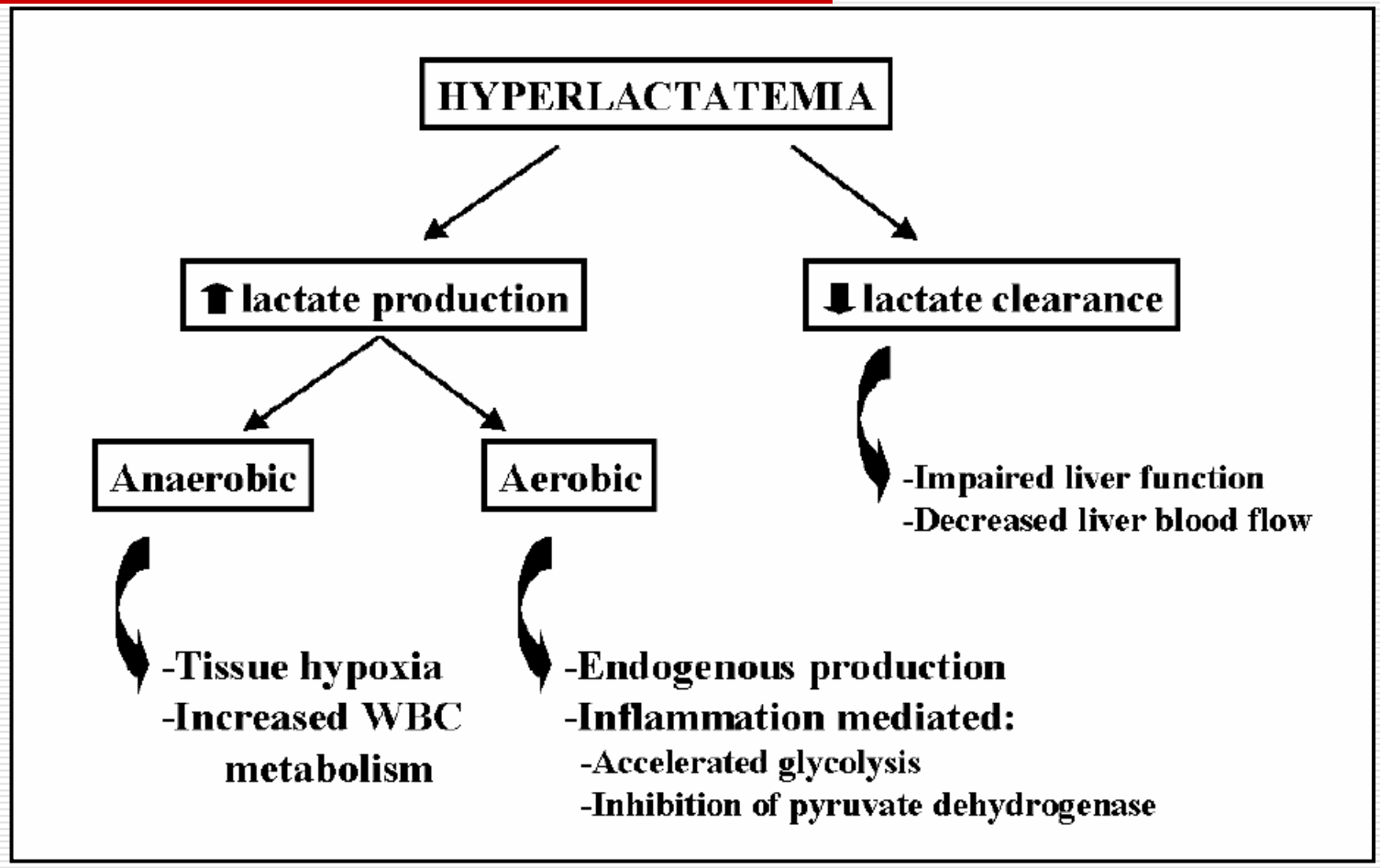


Clin Chest Med 1996; 17:249

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)
- Lactate production ↑ in lungs with inflammatory process. (Am J Resp Crit Care Med 1997; 156: 1099-1104)
- WBC metabolism largely anaerobic

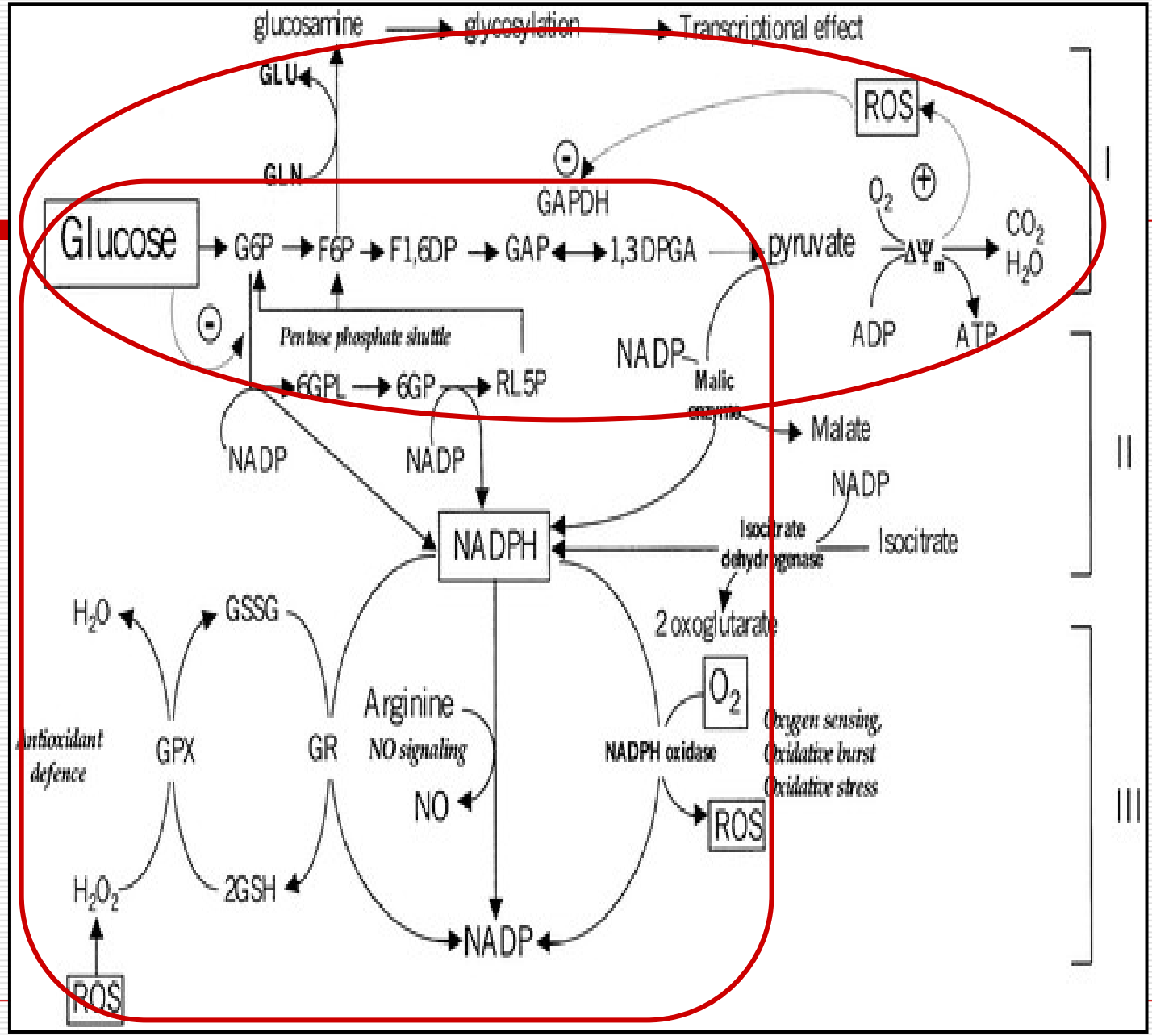
Lactic Acidosis & Sepsis



Intensive Care Med 2003; 29:699

Hyperglycemia - Reactive Oxygen Species

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



Intensive Care Med 2003; 29:511

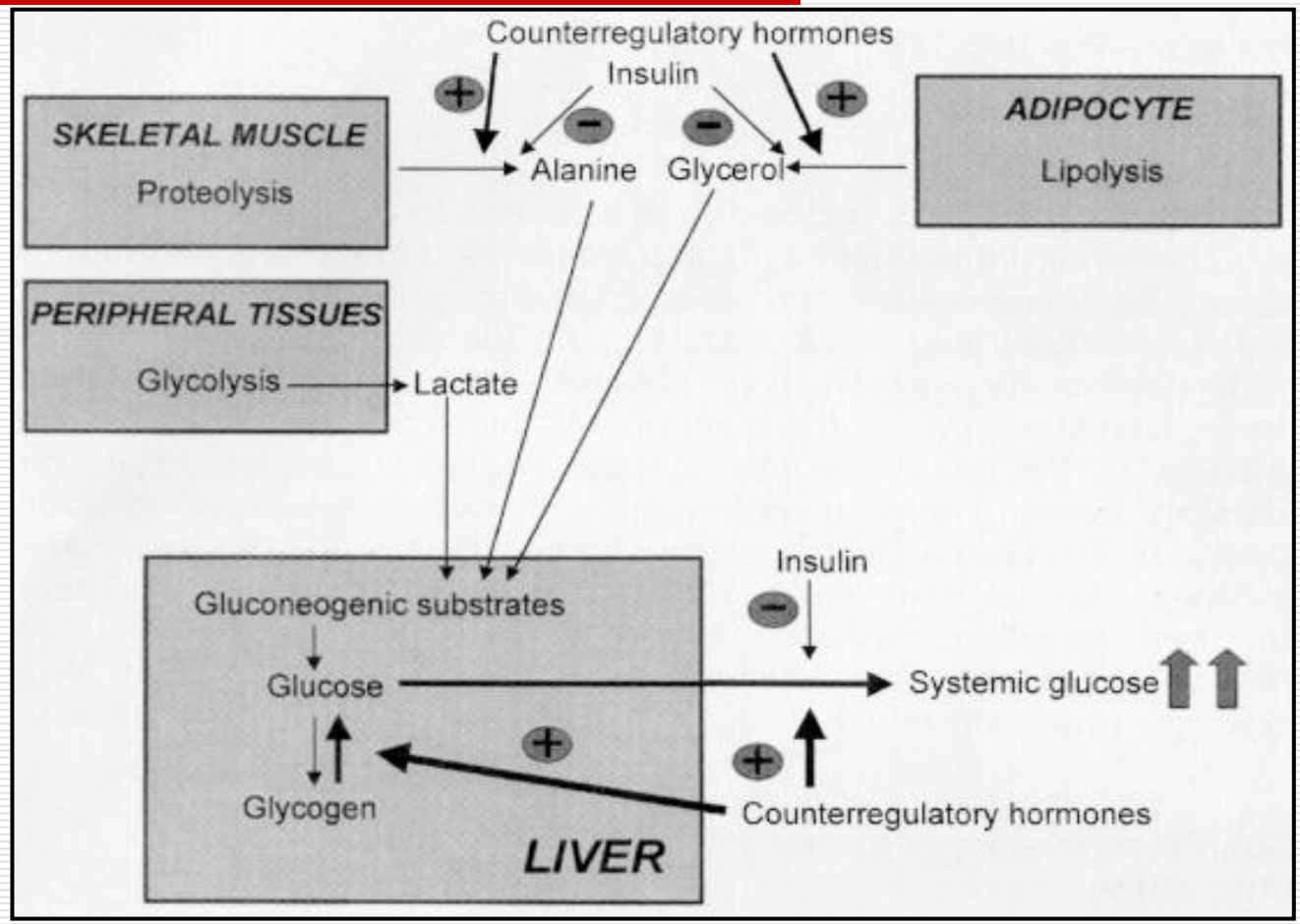
ROS

- Concentrated in
  - Phagocytic cells
    - macrophages, Kupffer cells & PMNs
  - Epithelial cells
    - enterocytes, hepatocytes, alveolar & renal tubular cells
- Leads to mitochondrial damage

ROS & Vulnerable Organs

- Intracellular hyperglycemia transported by GLUT1-3 (Brain, gut, liver, kidneys, immune cells) exacerbate mitochondrial superoxide formation
- Superoxide + NO → ↑ peroxynitrite
- Peroxinitrites → tyrosine nitration of proteins to alter function
- Mitochondrial damage likely leads to MSOF

Lipid & Muscle Metabolism during Stress

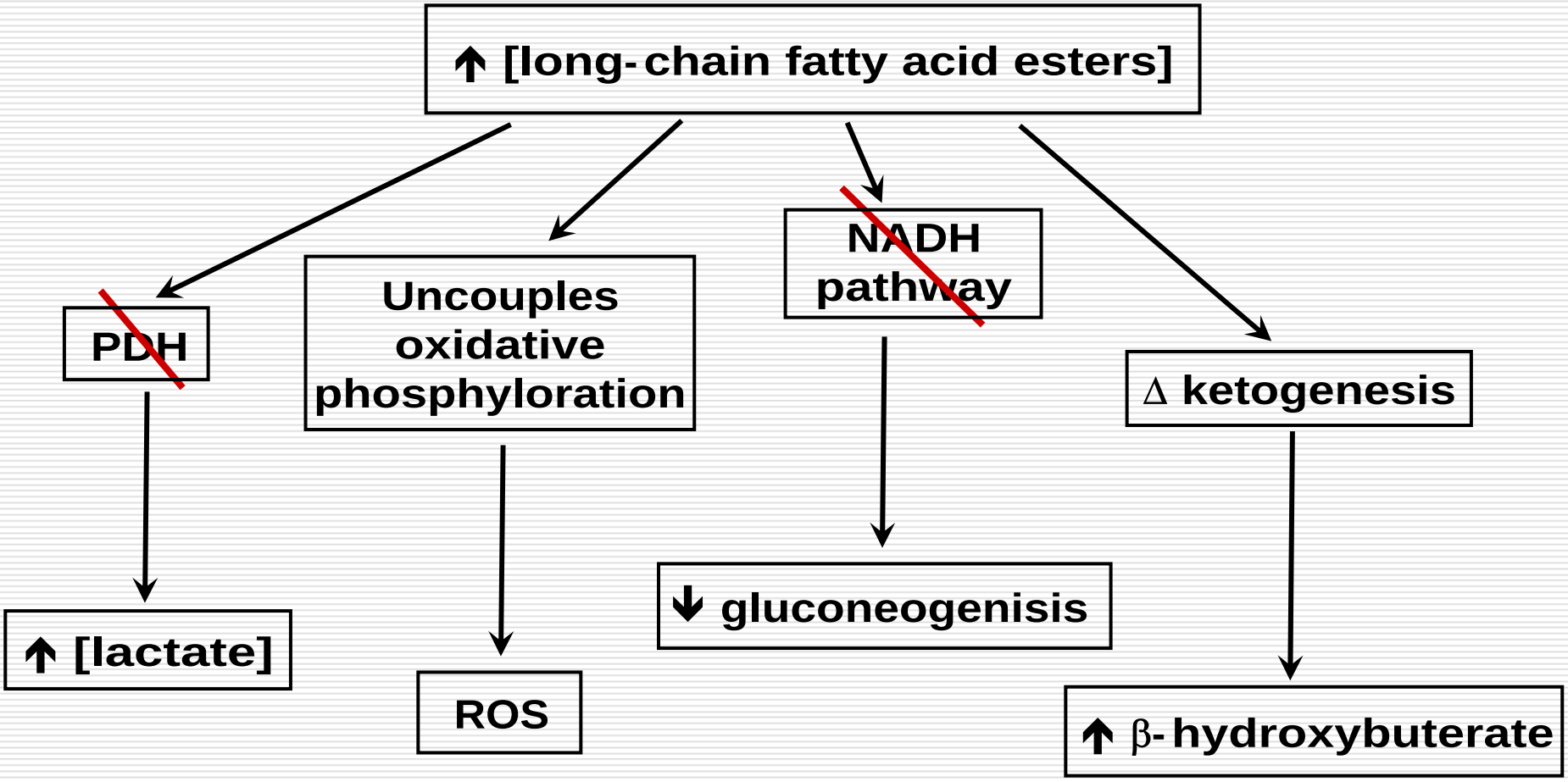


Crit Care Clin 2001; 17:107

Lipid metabolism

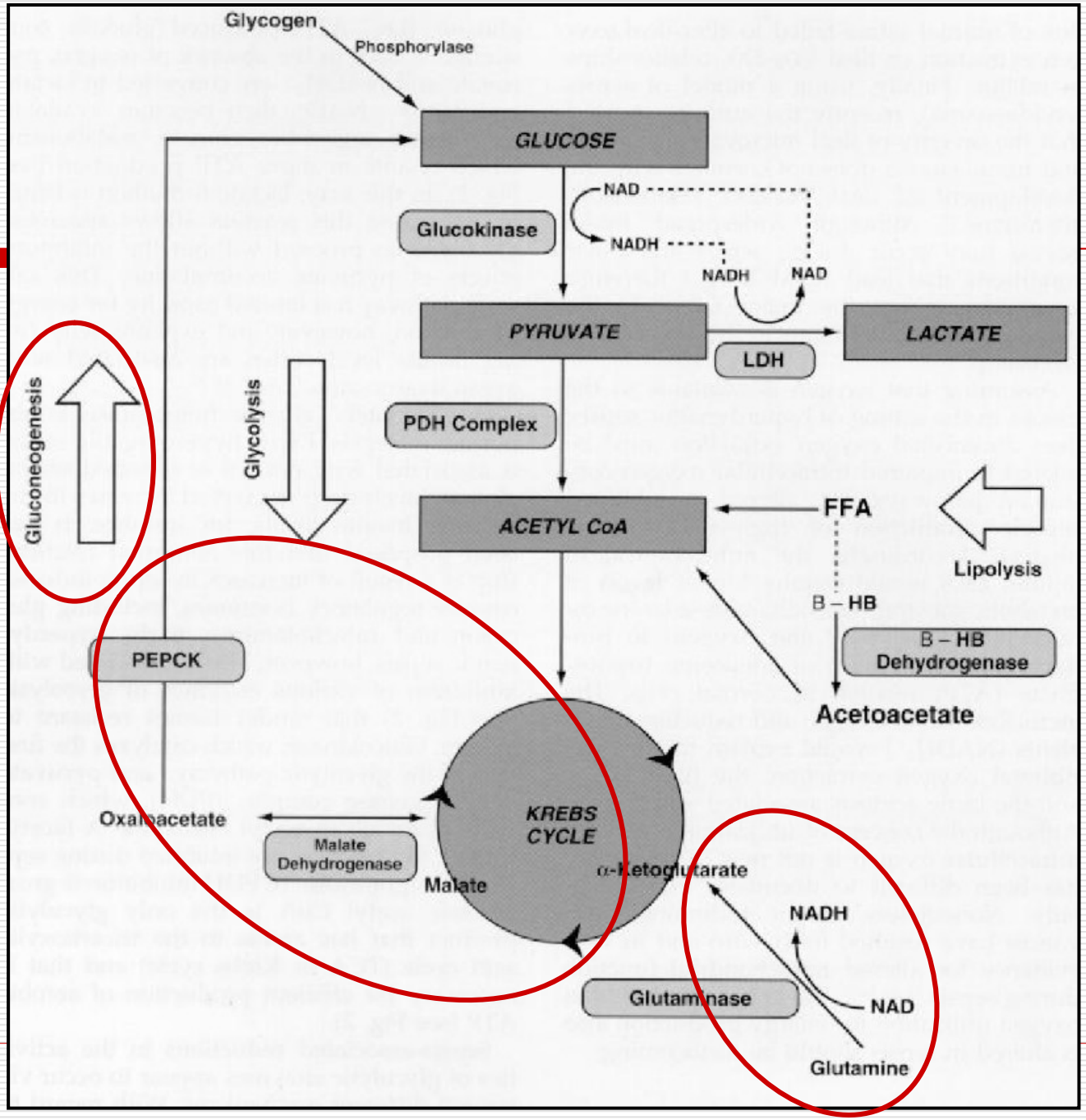
- ↑ FFA
- ↑ TG
- ↓ HDL, LDL
- Impaired intracellular transport of long chain FFA esters

Effects of Increased Intracellular [Long Chain FFA Esters]



Muscle Catabolism

- Muscle catabolism → alanine → glutamine
  - Muscle [glutamine] ↓ 80-90% with severe stress
- ↑ gluconeogenesis



Clin Chest Med
1996; 17:249

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 → ↑ 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 phosophenolpyruvate 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)

- Watson RS, *et al.* (Am J Resp Crit Care Med 2003: 167: 695-700)
- Annual incidence: 0.56/1000
- Highest in infants: 5.2/1000
- VLBW or other underlying disease
- Respiratory infection & bacteremia most common
- Mortality: **10.3%**
  - 4400 deaths per year

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