

Metabolic Changes Associated with Stress

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Starvation vs Cachexia

- Starvation - reversed by feeding
- Cachexia - metabolically driven
- Body weight inaccurate - failure to distinguish fat from lean body mass

Stress Injury and Metabolic Response

- Phases of injury and repair
- Measure effectiveness of metabolic interventions
- Implications associated with use of transthyretin

Stress Response

- Stress injury manifests a cytokine-mediated hypercatabolic response
- Catabolism is greatest from day 2-5 and
 - reflects the extent of injury
- Characterized by insulin-resistance

Cuthbertson's Phases

- Hemodynamic (ebb) phase: 12-24 hrs
- Catabolic flow phase:
 - Loss of lean body mass
 - Increased gluconeogenesis and lipolysis
- Anabolic flow phase: upsurge of IGF1

FLOW PHASE

- Immobilization and losses of S, N, P, Ca
- Urinary nitrogen loss as much as 27 g/24 hours
- hyperglycemia with gluconeogenesis

Flow Phase

- Insulin resistance -
counteregulatory hormones
- liver role in depressed pituitary-
thyroid axis and IGF1 production
 - acute phase reactants (APRs)
 - decreased binding-proteins (BPs)
- lipid dependency for non glucose
dependent tissue
 - Damaged tissues - reliance on
glycolysis

Metabolic Consequences

- REE and RQ increased
CO₂ ~ O₂ consumption
- VO₂ a guide to adequate O₂

Insulin resistance

- Catecholamine and glucagon
- Cortisol
- Growth hormone/without effect of IGF1

Hypercortisolemia

- mediated by IL-6
- decreased cortisol-binding globulin (CBG)
- increased production of cortisol
- amplification of effect by free ligand

Thyrometabolic status

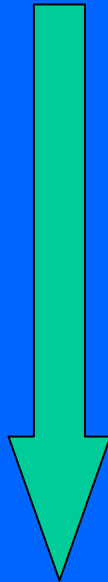
- Decreased TBG (normal FTI), normal TSH
- Halving of TTR in 48 hours
- Release of extrathyroidal T4 from liver (40%)
- Free T4 availability amplified

RBP and Retinoids

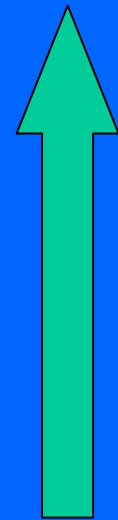
- RBP halved in 48 hours
- Release of retinoids from liver depots
- Availability of free ligand for wound healing

Binding Protein and Hormonal Change

- Albumin
- TBG
- CBG
- Transthyretin
- RBP
- IGF1-BP3



- free T4
- free Cortisol
- free T4
- free Retinol
- free IGF1



What This Means

- Transient decline in TTR & RBP: hyperthyroid & hyperretinoid state
- Pre-existing malnutrition IMPAIRS reactive response
 - Baseline of liver secretion is already low
 - Reflected in higher mortality rate

Albumin shortcomings

- Extravascular pool large (2/3)
 - *high albumin with dehydration
 - *low albumin with IV administration, chronic catabolic states, cirrhosis, CRF, protein-losing enteropathies

Ideal features of RTP

- Reflects early PCM changes
- follow increments over reasonably short period of time
- assess quality of response

*Bernstein LH. New marker of nutritional status. ACL pp20-23. 1989. Bernstein LH, Leukhardt-Fairfield CJ, Pleban W, et al. Clin Chem 1989. 35:271-4.

Transthyretin Levels

- < 5 mg/dl
- 5 to 10 mg/dl
- 11-17 mg/dl
- > 17 mg/dl

- Critical
- High risk
- Mild
- Normal

Malnutrition and Survival

- Weight loss associated with risk of infection and hospitalization
- Body cell mass depletion associated with shortened survival
- Low ratio of body cell mass to body weight associated with short survival

Nitrogen Death

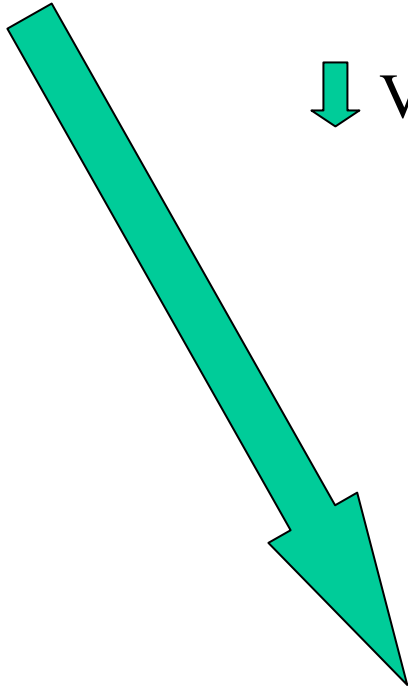
↓ Muscle mass

↓ Visceral proteins

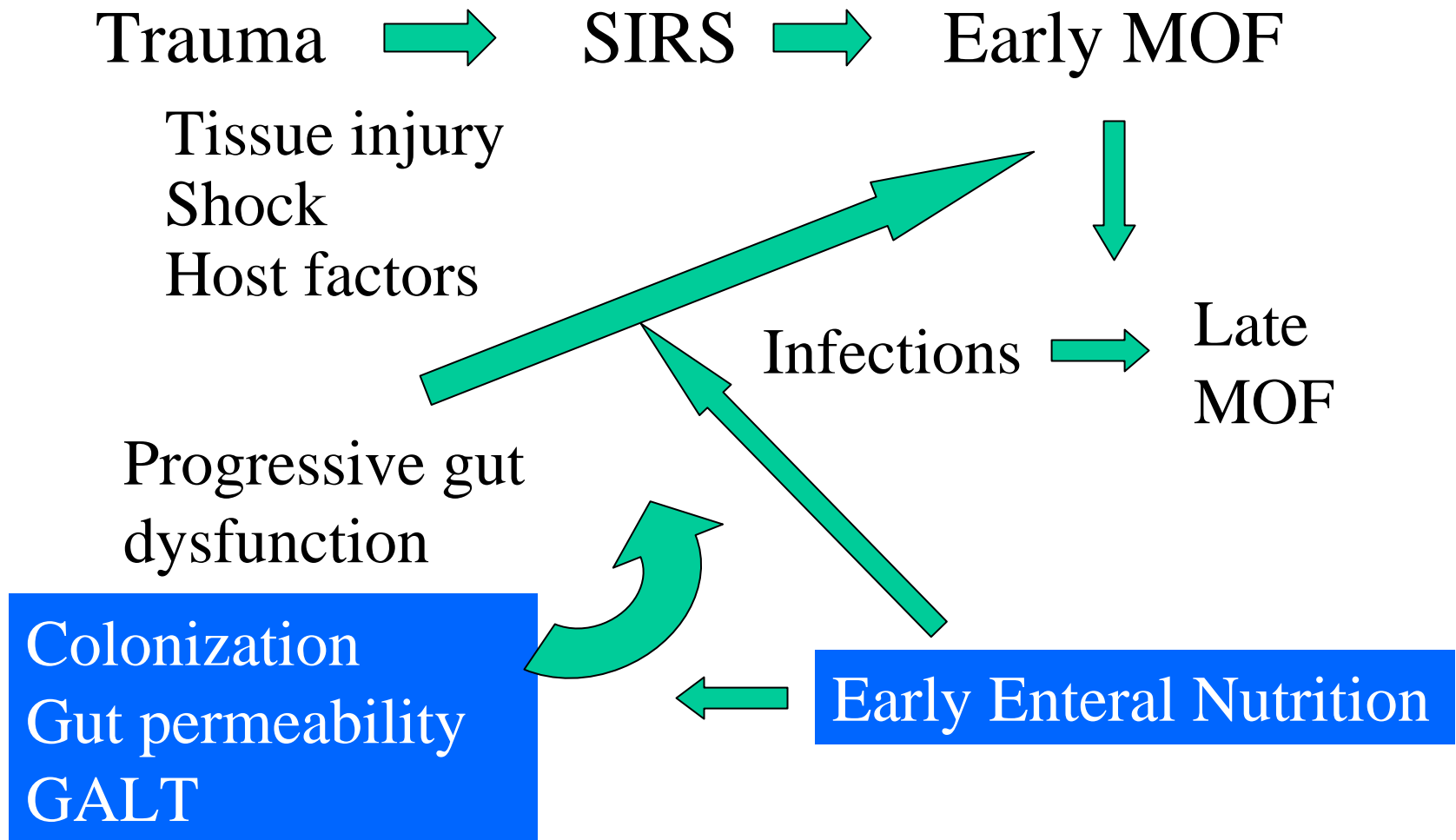
↓ Organ function

↓ Immune function

↓ Septic complication



Dysfunctional Inflammation



SIRS/Sepsis

- Temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
- Heart Rate $> 90/\text{min}$
- Respiratory rate $> 20/\text{min}$
- Pa CO₂ < 32 torr (< 4.3 kPa)
- WBC $> 12\text{k}$ or $< 4\text{k}$ cells/mm³
 $> 10\%$ bands

Indications for Nutritional Support

Critically-ill

Severely malnourished

Moderately stressed +
moderately malnourished

TNFI and Obesity

- TNFI mediates insulin resistance of obesity through overexpression in fat tissue
- Correlation between TNFI mRNA in fat tissue (2.5-fold) and
- level of hyperinsulinemia in obesity

Hotamisligil GS, et al. J Clin Invest 1995;95:2409-15

Protection from Obesity-Induced Insulin Resistance

- Mice lacking TNFI (obese, null mutation)
 - Insulin-resistance biggest factor in NIDDM
 - TNFI blocks insulin action
 - TNF null resulted in improved insulin-sensitivity in diet-induced and ob/ob model
- Uysal KT, et al. Nature 1997;389:610-14

Leptin Levels and Cirrhosis

- Leptin levels increased in cirrhotic patients
- Higher in cirrhotic than chronic hepatitis
- Leptin levels increase as liver function decreases

Testa R, et al. J Hepatol 2000;33:33-7

Leptin and Energy Expenditure

- Leptin levels in cirrhotics correlated with REE_xFFM
- Free leptin reflects fat mass
- Increased serum leptin related to bound leptin and correlated with REE

Ockenga J, et al. Gastroenterol 2000;119:1656-62

Leptin + TNF alpha

Macrophages have leptin receptors
Leptin/TNF alpha interaction
phagocytosis



altered cytokine production



TH2



TH1



Hepatotoxicity