Nutrition Therapy in Critical Illness

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Objectives

- Discuss the hypermetabolism of the systemic inflammatory response and how it relates to nutrition and metabolic response.
- Identify the uses of enteral nutrition to address nutritional and inflammatory issues.
- Demonstrate the inadequacies of traditional approaches to nutrition assessment, intervention, and monitoring.
Nutrition Support Therapy: Modulating the Stress Response and Systematic Immunity

Adjunctive Supportive Care

Proactive Primary Therapy
Rationale for Nutrition in the ICU

• Current Goals: "therapy not support"
  Evidence-based risk reduction
  – attenuate metabolic response
  – limit and reverse loss of lean body tissue
  – prevent oxidant stress
  – favorably modulate immune response

# Metabolic Comparisons: Stress vs. Starvation

<table>
<thead>
<tr>
<th></th>
<th>Starvation</th>
<th>Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>REE</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>RQ</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Primary Fuels</td>
<td>Fat</td>
<td>Mixed</td>
</tr>
<tr>
<td>Glucagon</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Insulin</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>↓</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Blood Glucose</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Ketogenesis</td>
<td>↑↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma Lipids</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Protein Synthesis</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Proteolysis</td>
<td>↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Urine Nitrogen Loss</td>
<td>↑</td>
<td>↑↑↑↑</td>
</tr>
</tbody>
</table>
Metabolic Changes to Stress: Resting Energy Expenditure
3 phases of metabolic response

• Ebb Phase = Stress (0-48 hours)
  – ↓ Cardiac Output
  – ↓ Tissue perfusion
  – ↓ Oxygen Consumption
  – ↓ REE

Nutritional Goal: Metabolic Support
3 Phases of metabolic response

• Flow Phase = catabolic (24+hours)
  – ↑ cytokines
  – ↑ Counterregulatory hormones and
    ↑ catecholamines
  – ↑ Insulin
  – ↑ O2 consumption, ↑ REE
  – ↑ Catabolism
    • Hyperglycemia, + fluid balance, - N balance
– Shift toward production of positive acute phase reactants
Nutritional Goal: Metabolic Support
3 Phases of Metabolic Response

- Repletion Phase = anabolic
  - Can last for months
  - May need up to 130% REE to support tissue repair, repletion, and recovery

Nutritional Goal: shift from metabolic support to promotion of repletion
Comparison of Measured Metabolic Rate

<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>Measured Metabolic Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1492 (RQ 1.0)</td>
</tr>
<tr>
<td>10</td>
<td>2015 (RQ 0.71)</td>
</tr>
<tr>
<td>17</td>
<td>1820 (RQ 0.85)</td>
</tr>
</tbody>
</table>
How can Nutrition affect Metabolic Response?

• Enteral preferred to Parenteral
• Early Initiation of Enteral Nutrition
• Appropriate macro and micronutrients
  – Avoid Under/overfeeding
  – Pharmaconutrients
• Meticulous glycemic control
Enteral is Superior to Parenteral
Human Studies: Enteral vs TPN
What Does the Data Show?

48 studies in adult populations (46 in English literature)
20 surgical, 9 critical care, 7 pancreatitis, 5 IBD, 3 Hepatic disease,
3 mixed populations

General conclusions: fewer infections, shorter hospital stay

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore</td>
<td>89</td>
<td>Trauma</td>
<td>↓ Infections</td>
</tr>
<tr>
<td>Kudsk</td>
<td>92</td>
<td>Trauma</td>
<td>↓ Infections</td>
</tr>
<tr>
<td>Hasse</td>
<td>95</td>
<td>Hepatic transplant</td>
<td>↓ Infections</td>
</tr>
<tr>
<td>Reynolds</td>
<td>96</td>
<td>GI surgery</td>
<td>↓ Infections</td>
</tr>
<tr>
<td>Shirabe</td>
<td>97</td>
<td>Hepatic resection</td>
<td>↓ Infections</td>
</tr>
<tr>
<td>Kalfarentzos</td>
<td>97</td>
<td>Pancreatitis</td>
<td>↓ Sepsis/Comp</td>
</tr>
<tr>
<td>Windsor</td>
<td>98</td>
<td>Pancreatitis</td>
<td>↓ MOF/SIRS</td>
</tr>
<tr>
<td>Gramlich</td>
<td>04</td>
<td>Meta-analysis</td>
<td>↓ infections</td>
</tr>
</tbody>
</table>
TPN risks:
Systemic Immune Suppression

- Mucosal atrophy/GALT atrophy
- Overfeeding and hyperglycemia
- IV Lipids
- Catheter Infections
Use of TPN in Critical Care

- EN always first choice for Nutrition Therapy
- Second choice depends on:
  - Timing:
    - First week - STD (NPO)
    - After first week - PN
  - Malnutrition (weight loss) - Priorities reversed
- No other options for IV fat source (Intralipid)
  - Omit if PN used over first week
- Minimal use of supplemental PN (no use first week)

Heyland (JAMA 1998; 280:2013), Braunschweig (AJCN; 74:534), McClave (JPEN 2009; 33:277)
## IV Lipids and Immune Function: Clinical Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>YR</th>
<th>N</th>
<th>Population</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garrel</td>
<td>95</td>
<td>43</td>
<td>Burn</td>
<td>High/Low</td>
<td>2x ↑ infection</td>
</tr>
<tr>
<td>Battisella</td>
<td>97</td>
<td>55</td>
<td>Trauma</td>
<td>+/- IV LCT</td>
<td>↑ infection</td>
</tr>
<tr>
<td>Waitzberg</td>
<td>97</td>
<td>x</td>
<td>Home TPN</td>
<td>Various</td>
<td>↓ WBC function</td>
</tr>
<tr>
<td>Furukawa</td>
<td>99</td>
<td>23</td>
<td>Esophag</td>
<td>IV LCT</td>
<td>↓ Immune function</td>
</tr>
<tr>
<td>Mayer</td>
<td>03</td>
<td>21</td>
<td>Sepsis</td>
<td>Omega 3 vs Omega 6</td>
<td>omega 3 ↓ inflammation</td>
</tr>
</tbody>
</table>
You Are What You Eat

Dietary ω-6 FA

Membrane phospholipids

Dietary ω-3 FA

Arachidonic acid

Eicosapentaenoic acid (EPA)
Docosahexaenoic acid (DHA)

Leukotrienes
(4 series)
Proinflammatory
Cell adhesive
Chemotactic

Prostanoids &
Thromboxanes
(2 series)
Aggregates platelets
Immunosuppressive

Prostanoids &
Thromboxanes
(3 series)
Antiaggregatory
Non-immunosuppressive

Leukotrienes
(5 series)
Anti-inflammatory
Nonadhesive

lipoxygenase
cyclooxygenase

You Are What You Eat
The Anti-Inflammatory Effects of Enteral Nutrition

- Enteral nutrition can directly affect inflamed intestine
- Enteral nutrition can blunt acute inflammatory reactants
- Enteral formulas can have direct effect on cytokine/adhesion molecule expression by intestinal epithelium

Sanderson JPEN, 2005; 25:S134
Early is Better than Later
## Early Enteral Feeding Meta-analysis

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>Study Parameters</th>
<th>Study Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marik. <em>CCM.</em> 2001.</td>
<td>Feeding &lt; or &gt;36 hr</td>
<td>15 studies 753 patients</td>
<td>↓ Infections ↓ LOS</td>
</tr>
<tr>
<td>Lewis. <em>BMJ.</em> 2001.</td>
<td>NPO vs &lt;24 hr</td>
<td>11 studies 837 patients</td>
<td>↓ Infections ↓ LOS ↑ Vomiting risk</td>
</tr>
<tr>
<td>Heyland. <em>JPEN.</em> 2003.</td>
<td>&lt;24 to 48 hr</td>
<td>8 studies</td>
<td>Trend to ↓ infections and mortality</td>
</tr>
</tbody>
</table>
“Effects of Early Enteral Feeding on the Outcome of Critically Ill Ventilated Medical Patients”

- ICU patients
- Retrospective review of prospectively collected data
- N=4049
  - 2537 patients fed < 48 hours
  - 1512 patients fed > 48 hours
- Propensity scoring system to control for confounding variables
- Conclusions:
  - 20% decrease in ICU mortality (18.1 vs 21.4%)
  - 25% decrease in hospital mortality (28.7 vs 33.5%)
  - Influence greatest in sickest patients
    - Beneficial effect noted despite increase in VAP

Artinian V et al Chest 2006;129:960-967
Effect of Early EN

- Local
  - Innate Immunity
  - Commensal Organisms

- Systemic
  - Acquired Immunity
  - Gut-Lung Conduit for Inflammation

Gut Associated Lymphoid Tissue (G.A.L.T.)

- BM, spleen, LN
  - $2.5 \times 10^{10}$ Ig producing cells
- Gut
  - $8.5 \times 10^{10}$ Ig producing cells
Quantity
Quantity

- Cumulative energy deficit correlated to: 1
  - Longer ICU stay
  - More days on mechanical ventilation
  - More complications

- Underfeeding 2
  - Lowest quartile (<6kcals/kg/day)
    - Increase risk bloodstream infections

- Overfeeding 3
  - Highest tertile (>66% recommended)
    - Highest mortality
    - Least likely to breath spontaneously at d/c
  - Middle tertile had best outcomes

Consequences of Underfeeding

• Respiratory dysfunction
  ↓ Respiratory muscle strength
  ↓ Ventilatory response
  ↑ Failure to wean

• Low transport proteins in the absence of inflammation

• Poor wound healing
Consequences of Overfeeding

- Hyperglycemia
- Electrolyte imbalances
- Fluid overload
- Hyperlipidemia
- Organ dysfunction
- Hypermetabolism
- Failure to wean (CO$_2$ retention)
Nutrient Delivery in Surgery and Critically Ill Populations

- Calories 20-35 kcal/kg/day
- Carbohydrates 3-6 mg/kg/min
  - 250-350 gm/day
- Protein 1.25 - 2.0 gm/kg/day
  - 80-150 gm/day
- Lipids 10-30% of total calories
  - Dependent on lipid composition
- Vitamins/minerals/trace elements
  - Adequate to meet needs
Pharmoconutrients

- Glutamine
- Omega 3 fish oils
- Arginine
- Anti-Oxidants
“Glutamine: role in gut protection in critical illness”

• Critical illness
  • Alteration of gut epithelial cell function
  • +/- data for bacterial translocation
  • Gut as a source of pro-inflammatory cytokines

• Therapy should be targeted at
  • Protect epithelial from cell injury
  • Attenuate the elaboration of proinflammatory mediators via gut based immune cells

Proposed mechanisms for glutamines ability to attenuate the SIRS response

- Tissue protection
  - Heat shock protein
  - Anti-apoptotic effect
  - Fuel source for epithelial cells
- Anti-inflamatory
  - Attenuate NFkB
  - Enhanced PPAR activation
  - Attenuation of cytokine expression
- Preservation of tissue function in stress states
  - Preserves ATP in sepsis and I/R
  - Preserves mitochondrial function
- Antioxidant
  - Enhanced GSH
  - Attenuates iNOS in sepsis and I/R
  - Reduction in oxidant stress

Enteral Feeding with EPA+GLA
Clinical Outcomes Summary

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Improved oxygen status</th>
<th>Reduced ICU LOS</th>
<th>Less time on vent</th>
<th>Fewer new organ failures</th>
<th>Reduced mortality</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
<td>X 2,3,5</td>
<td>X 2,3</td>
<td>X 3</td>
<td>X 2,3</td>
<td></td>
<td>▲ 2,3,5</td>
</tr>
<tr>
<td>ALI</td>
<td>X 6</td>
<td>X 6</td>
<td>X 6</td>
<td>X 6</td>
<td></td>
<td>▲ 6</td>
</tr>
<tr>
<td>Sepsis</td>
<td>X 1</td>
<td>X 1</td>
<td>X 1</td>
<td>X 1</td>
<td></td>
<td>▲ 1</td>
</tr>
<tr>
<td>Pediatric Burn</td>
<td>X 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▲ 4</td>
</tr>
<tr>
<td>Pediatric ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▲ 7</td>
</tr>
</tbody>
</table>


X = statistically significant
▲ = EPA+GLA diet was found to be safe in these patient populations.
Safety variables measured were no different from the control group.
Typical ALI/ARDS Inflammatory Response

Precipitating event
- Increase in neutrophil recruitment

Proinflammatory eicosanoids and free radicals produced

Pulmonary inflammation with loss of surfactant, edema and vasoconstriction

Impaired gas exchange and poor oxygenation

Leading to deterioration of patient’s condition
Immune Cell on Normal Lipids

Arachinodic Acid - Proinflammatory compounds

Phospholipid Membrane
Immune Cell on Special Fatty Acids

GOAL:
Less AA in cell membrane
Arginine

- Necessary for normal T lymphocyte function
- Myeloid suppressor cells regulate availability of arginine
- Myeloid suppressor cells are capable of causing states of severe arginine deficiency which impact production of nitric oxide
- Process is paralyzed during trauma and surgery - appears to be an arginine deficiency
  - But NOT during sepsis!!! (when arginine metabolized, NO is produced)

(Popovic J. Nutr. 2007; 137:1681S)
QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.
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Monitoring Nutrition Therapy in Critical Care

- Indirect Calorimetry
- Albumin
- PreAlbumin
- Nitrogen Balance
Indications for Conducting RMR Measurements

- Inability to estimate energy expenditure with accuracy
- Inadequate clinical response using predictive equations
- Possible signs of malnutrition
- Possible signs of overfeeding
Indirect Calorimetry

• Measure change in concentration of inspired oxygen (vO₂ in ml/min) and carbon dioxide excretion (vCO₂ in ml/min) to determine resting metabolic rate (RMR)

• RMR (kcal/d) = \{VO₂ (3.94) + VCO₂ (1.11)\} * 1.440
  – Abbreviated Weir equation

• Respiratory Quotient RQ = vCO₂/vO₂
## Traditional View of RQ

<table>
<thead>
<tr>
<th>Substrate Utilization</th>
<th>RQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>0.67</td>
</tr>
<tr>
<td>Fat oxidation</td>
<td>0.71</td>
</tr>
<tr>
<td>Protein oxidation</td>
<td>0.82</td>
</tr>
<tr>
<td>Mixed substrate oxidation</td>
<td>0.85</td>
</tr>
<tr>
<td>Carbohydrate oxidation</td>
<td>1</td>
</tr>
<tr>
<td>Lipogenesis</td>
<td>1-1.2</td>
</tr>
</tbody>
</table>
Nutritionally Associated Increased Carbon Dioxide Production: Excess Total Calories vs. High Proportion of Carbohydrate Calories

- 20 mechanically ventilated patients in Pulmonary Intensive Care Unit
- Compare VCO\textsubscript{2} from isocaloric nutritional regimens with varying concentrations of carbohydrates with VCO\textsubscript{2} from low and high caloric nutritional regimens with constant concentrations of carbohydrates.
- Results:
  - VCO\textsubscript{2} did not change with increasing CHO proportion.
  - VCO\textsubscript{2} increased with increasing total calories (p < 0.05).
- Conclusions:
  - High caloric feeding increases VCO\textsubscript{2} in contrast to high percentage carbohydrate formulation. Thus moderate caloric intake appears to be more important in avoiding nutritionally related increases in VCO\textsubscript{2}.

Talpers SS 1992; Chest 102:551-55
“Clinical Use of the Respiratory Quotient Obtained from Indirect Calorimetry”

• Prospective, multicenter study
• Determine the clinical use of RQ for monitoring adequacy and tolerance of nutrition support
• Results:
  – Total of 263 long-term acute care adult patients receiving nutrition therapy
  – Ratio of calories provided/required correlated with overall measure RQ ($p < .0001; R^2 = .16$)
  – Measured RQ compared to predicted reference RQ failed to differentiate appropriate from inappropriate feeding
  – Increasing RQ correlated with increasing respiratory rate ($p = .002, R^2 = .04$) and decreasing tidal volume ($p = .002, R^2 = .04$)

McClave SA et al. JPEN, 2003;27:21-26
Conclusion: Interpreting the RQ in Indirect Calorimetry

- If < 0.7
  - Prolonged fast > 16 hrs
  - Ethanol metabolism

- If > 1.0
  - Recent excess caloric intake

- RQ is a good marker of test validity (human biological range = 0.67-1.3)
- RQ doesn’t always reflect substrate use:
  - Inter-patient variability
  - The stress response
  - Underlying lung disease
  - Acid/base disturbances
  - Pharmacologic agents: propofol

McClave SA et al. JPEN 2003;27:21-26
Protein Markers

- Albumin, Prealbumin, Transferrin, Retinol Binding Protein
- Reflection of the acute phase response
  - Increases permeability and reprioritization of hepatic protein synthesis
- **DO NOT** accurately represent nutrition status in critical care setting
C-Reactive Protein

- Positive acute phase reactant - IL-6 stimulates release of CRP from liver
  - “hepatic reprioritization”
- Can be used to help interpret albumin/prealbumin values
Biomarkers of Inflammation

<table>
<thead>
<tr>
<th></th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PAB</strong></td>
<td>4</td>
<td>4</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>18.3</td>
<td>17.9</td>
<td>6.7</td>
<td>2</td>
</tr>
</tbody>
</table>
Nitrogen Balance

• 1 gm nitrogen = 6.25 gm protein
• N2 Balance = N2 intake – N2 output
• Determine anabolic (+ N2 balance) vs. catabolic state (- N2 balance) vs. equilibrium
• Factors:
  – Renal function: creatinine clearance of >40mL/min, or s.Creat <2.5 required to be accurate
  – Wound, fecal, high output fistula losses
Nitrogen Balance

- Necessary data:
  - 24 hour urine collection, volume in mL
  - Urine urea nitrogen (UUN) in grams
  - Accurate I/O’s essential and calorie count
- Nitrogen intake = 24 hour protein intake / 6.25
- Nitrogen output = 24 hour urine volume x UUN / 100,000
  plus obligatory losses (generally 3-4 gm/day)
Nitrogen Balance

• **Limited Validity**
  - Adequacy of urine collection
  - Unrecorded nitrogen losses from large open wounds, severe burns, diarrhea, or renal or liver failure
  - Ideally should be measured in “steady state” (impossible in critically ill)
  - Interpret values based on patient’s clinical status (i.e. inflammatory state)
A Vicious Cycle

- Inflammation and malnutrition both reduce transport protein concentrations by decreasing its rate of synthesis.
- Inflammation is associated with greater fractional catabolic rate of transport proteins.
- Inflammation promotes transfer of albumin out of the vascular compartment.
- Vicious cycle of inflammation results in anorexia with decreased effective use of dietary protein and augmentation of catabolism.
If sources of inflammatory mediators are not controlled, nutrition support will not preserve catabolic lean tissue!!!

Kudsk, Trauma 5 ed., 2004
In Conclusion:

• Feed enterally - do everything possible to use the gut!
• Start enteral nutrition within 24-48 hrs
• Give the right amount - can cause more metabolic stress - use IC
• Pharmaconutrients
  – Glutamine: gut protection
  – Omega-3: ARDS/ALI/Sepsis
  – Arginine: trauma/surgery (avoid sepsis)
• There is no accurate measure of nutrition in critically ill
References


“OK this time, but tomorrow you’re going on a diet!”