Protein Delivery in the Critically Ill Patient

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Objectives

- Discuss rationale for adequate protein delivery in critically ill patients
- Present barriers to providing adequate protein
- Discuss potential solutions for improving protein delivery to critically ill patients
~1/3 of patients malnourished on hospital admission
- If left untreated, 2/3 will further decline
~1/3 of patients become malnourished during hospitalization

Tappenden KA, et al. JPEN 37:482-497
Hospital Malnutrition

Adverse Effects on Patient:

- Morbidity
- Mortality
- Hospital Length of Stay
### Metabolic Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Starvation</th>
<th>Stress</th>
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<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>
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<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>
Clinical Consequences Metabolic Stress

- Hypermetabolism
- Hypercatabolism
  - 12 to 35 gm Nitrogen/day (75-129 gm protein)
- Hyperglycemia
- Peripheral Insulin resistance (~50% ↓)
- Fluid & electrolyte changes
Clinical Consequences of Protein Catabolism

- ↓ Visceral proteins
- ↑ Acute phase proteins
- ↓ Coagulation capacity
- Impaired immune response/ ↑ Infection rate
- Impaired wound healing
- Altered gut function
- Skeletal muscle wasting
- ↓ Muscle function / ↑ Weakness
  - Inhibits sufficient cough, prolongs vent need
Contributors to Protein Loss

- Metabolic insult
- Paralyzing agents
- Sedation
- Bed rest
- Inotropic support
Protein Mass Loss in Critical Illness

Who is affected?

- ICU short stay (24-48 hr)
  - LBM loss minimal effect on outcome
- Severe Sepsis (1)
  - First 10 d - 67% from skeletal muscle
  - > 10 d – from viscera
  - 1.8 kg of protein
- Blunt trauma (2)
  - First 15 d – 70% from skeletal muscle
  - 0.5 kg of protein in 8 days
- Critical surgical illness (3)
  - Large nitrogen losses
  - Not much cardiac mass and function loss

Protein Turnover in Critical Illness

- Increased protein breakdown
  - (25-127%)

- Increased whole body protein synthesis
  - (16-47%), varies between tissues
  - Acute phase response, wound repair, immune response, etc)

- Negative protein balance

- Increased amino acid flux from periphery to liver

Energy Intake on Patient Outcome

- Negative energy balance = negative effects on outcome in ICU patients
  - Increased infectious complications (1)
- Meta-analysis (2)
  - Early EN = Reduced:
    - Infection risk
    - Hospital LOS
- Meta-analysis (3) – inconclusive
- Studies with energy intake on protein mass & turnover vary
  - disease type, nutritional status, type of feeding

Nutritional support may limit, but not stop loss of body protein mass in Critical Illness
Protein Intake on Patient Outcome?
Table 1 Overview of relevant studies with protein delivery and outcome in mechanically ventilated critically ill patients.

<table>
<thead>
<tr>
<th></th>
<th>EPaNIC</th>
<th>TICACOS</th>
<th>SWISS</th>
<th>EDEN trial (Pilot-200 points)</th>
<th>EDEN trial (Full MCT-1000 points)</th>
<th>Arubi trial</th>
<th>Alberda International Critical Care Nutrition Survey</th>
<th>Weijs Dutch trial</th>
<th>Allingstrup trial (Danish)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU LOS (Median)</td>
<td>3.5</td>
<td>12</td>
<td>ICU LOS &gt;5 days</td>
<td>13.1</td>
<td>12</td>
<td>19</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital LOS (Median)</td>
<td>15</td>
<td>25</td>
<td></td>
<td></td>
<td>68.7</td>
<td>24.2</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mech. vent days (Median)</td>
<td>2</td>
<td>10.75</td>
<td>5.6 days (mean vent days in survivors)</td>
<td>11.9</td>
<td>9.0</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>6.2%</td>
<td>25.4%</td>
<td>ICU LOS &gt;5 days</td>
<td>20.4</td>
<td>19.6</td>
<td>22.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>10.6%</td>
<td>38.3%</td>
<td>ICU LOS &gt;5 days</td>
<td>34.4%</td>
<td>21%</td>
<td>36%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-discharge</td>
<td>11.2%</td>
<td>47%</td>
<td>ICU LOS &gt;5 days</td>
<td>29.1%</td>
<td>23%</td>
<td>22.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (mean, unless indicated)</td>
<td>51.6%</td>
<td>28.45</td>
<td>26.15</td>
<td>28.7</td>
<td>30</td>
<td>28.5</td>
<td>&lt;25, &gt;35 for optimal benefit of calorie delivery</td>
<td>26</td>
<td>25.6</td>
</tr>
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<td>&lt;25, &gt;35 for optimal benefit of calorie delivery</td>
<td>26</td>
<td>25.6</td>
</tr>
<tr>
<td>Protein delivery</td>
<td>&lt;60g per day - both groups</td>
<td>Study-76 g per day (~1.0 g/kg per day)</td>
<td>Full energy - 54 g per day</td>
<td>Not reported in article</td>
<td>Full feed - 43.6 g per day</td>
<td>Recommended</td>
<td>Protein - energy target: 89 g per day (1.31 g/kg per day)</td>
<td>Mean protein delivery by group:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Mean: 0.8 g/kg after 3 days)</td>
<td>Cont-53 g per day (0.68 g/kg per day)</td>
<td>Trophic-11 g per day (1st 7 days then ~50 g per day)</td>
<td><del>0.6</del>0.8 g/kg per day in full feeding group and after 7 days in both groups</td>
<td>Underfed - 47.5 g per day</td>
<td>1.5~2.0 g/kg per day</td>
<td>Energy target: 78 g per day (1.06 g/kg per day)</td>
<td>High protein- 1.46 g/kg per day</td>
<td></td>
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<tr>
<td></td>
<td>~0.8 g/kg per day for both groups after 7 days</td>
<td>[Personal communication-T. Rice [primary author]]</td>
<td>[Mean: ~0.6 g/kg per day for both groups]</td>
<td>[Mean: ~0.6 g/kg per day for both groups]</td>
<td>No target = 67 g per day</td>
<td>Medium protein- 1.06 g/kg per day</td>
<td>(0.83 g/kg per day)</td>
<td>Low protein-0.79 g/kg per day</td>
<td></td>
</tr>
<tr>
<td>Clinical benefit of</td>
<td>(-)</td>
<td>(+) - Mortality</td>
<td>(+) - Infection</td>
<td>(-)</td>
<td>(-)</td>
<td>(+) - Mortality</td>
<td>(+) - Mortality hazard for reaching protein and energy target</td>
<td>(+) - Mortality hazard for increased protein delivery</td>
<td></td>
</tr>
<tr>
<td>SPN or additional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>calorie/protein</td>
<td>delivery</td>
<td></td>
<td></td>
<td></td>
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</table>

More limited data for the Swiss trial due to only abstract data being available. EDEN trials utilized ICU-free, Hospital-free, and Mech. vent-free days as outcome measures so more limited comparison data are available. EPaNIC, Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients.
Arabi Trial

- RCT permissive underfeeding (60-70%) energy target vs target feeding (90-100%)
- Harris-Benedict equation + stress factors
- Actual energy intake
  - 59% (1067 kcal) vs 71% (1252 kcal)
- Protein intake: 0.6 g/kg/d
- No difference:
  - Mortality: ICU, 28-day, 180-day
  - ICU LOS, infection rate
- Difference: Hospital mortality with permissive underfeeding

EDEN Trial

- PRT, ALI patients (age: 52 yr)
- Average BMI: 30
- Trophic vs full feeding first 6-days intervention
- Actual energy intake:
  - 25% (400 kcal) vs 80% (1300 kcal) target
  - Attained Study day 1 (pts included within 72hr intubation)
- Actual protein intake: 0.6-0.8 g/kg/day
- No Difference:
  - Mortality: 60-day, ventilator-free days, infection rate
- Less GI complaints trophic feeds
- Summary: 25% energy target during first 6-days doesn’t affect outcomes vs 80% energy target
- Received ~50% protein needs, were likely not deficient in LBM

Observational study (n=113)
Critically ill septic patients
Energy & protein via indirect calorimetry and nitrogen excretion
Protein provided as: 0.8, 1.0, 1.4 g/kg/d
Reduction in:
  - Mortality with increased protein
  - Energy no effect

ICU patients with mechanical ventilation >72 hrs (n=2772, 165 ICUs)
- Inverse relationship between odds of mortality and total calories received
- Benefited BMI <25 and >35
- Feeding +1000 kcal nearly halved odds of 60-day mortality (p=.014)

Similar results with feeding additional 30gm of protein

? LBM critical for ICU outcomes

BMI <25 and >35 insufficient LBM reserves to optimally survive ICU stay without more aggressive energy and protein provision?

Summary

- Energy target may not be most important nutritional target to meet
- Difficult to determine effect of energy versus protein
- Administration of amino acids or protein improves total body protein mass and protein turnover in critical illness
- Doses of 1.2-1.5 g/kg body weight/day
Guidelines

- SCCM/ASPEN
  - 25-30 kcal/kg/day, Protein: 1.2-2.0 g/kg/day
  - Obesity
    - Energy
      - 60-70% target energy requirements
    - Protein:
      - BMI 30-40, ≥2.0 gm/kg IBW/day
      - BMI >40, ≥2.5 gm/kg IBW/day

- ESPEN
  - 20-25 kcal/kg/d [first 72-96 hr], then up to 25-30 kcal/kg/d
  - No mention of protein enterally, parenteral 1.3-1.5 g/kg/d IBW

- European Society of Intensive Care Medicine
  - Cautions against > 1.8gm/kg/d

- American Burn Association
  - Protein varies: 1.5-3.0 gm/kg/d
What’s the Reality??
Failure to Provide Adequate Nutrition

WHY?

- Worldwide survey (1)
  - Energy and protein delivery ~45-55% of prescribed
- Poor volitional intake
- Financial concerns
- Advanced stage of disease
- Low priority
- Lack of knowledge or screening
- Controversial clinical outcomes

1. Sinuff t, et al. JPEN, 34:660, 2010
Weight and LBM Loss During Hospitalization

WHY??

- Metabolic stress and consequences
- No nutrition intervention – procedures, overlooked
  - EN commonly fails to achieve >50% protein goal
- Pain (general, abdominal)
- Incontinence
- Nausea, vomiting
- Depression
- Feeding difficulties
- Unpalatable foods, altered feeding schedules
- Inadequate Diets
Pt made NPO upon admission
HD 3 – diet ordered
HD 5 – NPO for OR
POD 4 (HD 9) same diet for 3 days

- **Clear Liquid Diet with Restrictions:**
  No concentrated sweets, low sodium

Patient received
- Low sodium broth
- Sugar-free jello
- Diet soda
- Unsweetened coffee and tea
### Table 1. Protein Intake Inspired by Recent Prospective Nutrition Studies in the Intensive Care Unit.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Protein Intake in Control Group</th>
<th>Protein Intake in Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Berghe et al,(^9) g/kd/d</td>
<td>0.85</td>
<td>0.80</td>
</tr>
<tr>
<td>Rice et al,(^{10}) g/d</td>
<td>11</td>
<td>54</td>
</tr>
<tr>
<td>Arabi et al,(^{11}) g/d</td>
<td>47.5</td>
<td>43.6</td>
</tr>
<tr>
<td>Singer et al,(^{12}) g/d (g/kg/d)</td>
<td>53 (0.68)</td>
<td>76 (1)</td>
</tr>
<tr>
<td>Heidegger et al,(^{13}) g/d</td>
<td>56</td>
<td>79</td>
</tr>
<tr>
<td>Casaer et al,(^{14}) g/d</td>
<td>&lt;60</td>
<td>&lt;60</td>
</tr>
<tr>
<td>Weijs et al,(^{8}) g/d</td>
<td>67</td>
<td>89</td>
</tr>
</tbody>
</table>

Adapted from Singer and Pichard.\(^{25}\)

What’s Happening?

- Main target nutrition prescriptions on energy requirements
- Protein intake secondary target
- If enteral formulas provide energy target, many not meeting protein target
- Lack of ability to evaluate nitrogen needs
  - ? Choose markers according to main aims of AA provision
  - Ex: if LBM is targeted – dual-energy x-ray absorptiometry, bioimpedance, magnetic resonance imaging measurements
  - Ex: glutamine supplementation – oxidative stress, glutathione measurement
What Can Be Done?

- Collaboration amongst multiple clinical disciplines
- Protocols
  - High protein feedings
  - Supplement protein until energy targets met
- Add protein supplements:
  - to low protein diets (ex: Clear Liquids)
  - Until oral diet fully tolerated
- Use liquid protein supplements to provide oral medications [Med-Pass]
Summary

- Malnutrition not just energy deficiency
- Protein key macronutrient for improving patient outcomes
- Important to maximize delivery early and maintain
- Interdisciplinary approach
- Education and awareness key to success
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