Are Your Patients Getting the Protein They Need?

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Regional One Health  
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Disclosures

• Speaker, Nestlé Health Science  
• Consultant, Fresenius-Kabi

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Objectives

- Evaluate how calories and protein work together
- Discuss the evidence regarding the importance of protein delivery to optimize clinical outcomes for the critically ill patient
- Address protein requirements across the ICU spectrum
- Apply hypocaloric, high protein feeding in critical illness

Influence of Caloric and Protein Intake Upon Nitrogen Balance


*TPN @ 2000 to 2500 kcals/d + 1.7 g/kg/d overall; 1.3 ± 0.5 g/kg/d during study
The Impact of Energy Balance Upon Nitrogen Loss After Traumatic Injury

<table>
<thead>
<tr>
<th></th>
<th>Hypercal</th>
<th>Eucaloric</th>
<th>Hypocal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td><strong>Energy in</strong> (% of REE)</td>
<td>148 ± 19</td>
<td>118 ± 20</td>
<td>82 ± 16</td>
</tr>
<tr>
<td><strong>Protein in</strong> (% of REE)</td>
<td>22 ± 3</td>
<td>22 ± 4</td>
<td>22 ± 5</td>
</tr>
<tr>
<td><strong>Nit Bal g/d</strong></td>
<td>-8.3 ± 5.7</td>
<td>-7.5 ± 5.2</td>
<td>-7.9 ± 5.5</td>
</tr>
<tr>
<td><strong>Urine 3-meH umol/d</strong></td>
<td>375 ± 95</td>
<td>422 ± 180</td>
<td>347 ± 147</td>
</tr>
</tbody>
</table>


Excessive Caloric Delivery Increases Fat Mass Without Changes in Lean Body Mass in Thermally Injured Patients

![Graph showing the relationship between caloric balance and changes in fat mass and lean body mass](image)

Loss of Body Cell Mass During Critical Illness:  
A Theoretical Analysis

- 80 kg well nourished man (~64 kg BCM)
- NBAL = -20 g/d (No protein intake)
- 1 g loss with NBAL = ~ 32 g BCM
- 20 g loss with NBAL = 640 g/day BCM
- Death occurs at ~25 to 30% loss of BCM or 16 to 19 Kg loss of BCM
- Death from starvation in ~20-25 days (normal ~60 days)

Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS\(^{1-3}\)

*Donald P Kotler, Anita R Tierney, Jack Wang, and Richard N Pierson, Jr*

Which Is More Important During Critical Illness?

The Importance of Protein Delivery During Critical Illness

• 886 mixed med-surg ICU patients, initiated EN within 24hrs, > 7d nutrition, observational
• Target: 1.3 X BEE, then 1.1 X mREE + 1.2 – 1.5 g/kg/d protein
• Protein grp not analyzed due to low pt number

<table>
<thead>
<tr>
<th>Target Achievement</th>
<th>None</th>
<th>Prot &amp; Energy</th>
<th>Energy</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>412</td>
<td>245</td>
<td>205</td>
<td>24</td>
</tr>
<tr>
<td>Energy (kcal/d)</td>
<td>1572 ± 404</td>
<td>1897 ± 359</td>
<td>1819 ± 333</td>
<td>1898 ± 384</td>
</tr>
<tr>
<td>Energy (% target)</td>
<td>74 ± 15</td>
<td>99 ± 9</td>
<td>96 ± 5</td>
<td>85 ± 4</td>
</tr>
<tr>
<td>Protein (g/kg/d)</td>
<td>0.83 ± 0.23</td>
<td>1.31 ± 0.18</td>
<td>1.06 ± 0.14</td>
<td>1.21 ± 0.15</td>
</tr>
<tr>
<td>PN (% of patients)</td>
<td>18%</td>
<td>38%</td>
<td>30%</td>
<td>38%</td>
</tr>
<tr>
<td>Hyperglycemic index</td>
<td>110</td>
<td>1.32 ± 0.57</td>
<td>1.11 ± 0.45</td>
<td>1.19 ± 0.51</td>
</tr>
<tr>
<td>28 d Mortality (%)</td>
<td>20%</td>
<td>15%</td>
<td>20%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Provision of protein and energy in relation to measured requirements in intensive care patients
Matilde Jo Allingstrup a, Negar Esmaïlzadeh a, Anne Wilkens Knudsen a, Kurt Espersen a, Tom Hartvig Jensen b, Jørgen Wiis b, Anders Perner b, Jens Kondrup b

113 eligible mixed ICU pts (sepsis -85%), burns
Observational design
• Targets: 25-30 kcal/kg/d and 1.2-1.5 g/kg/d until mREE and NBAL
• EN + PN w/in 24 hr
• REE 120 to 150% BEE (~28 kcal/kg/d for each group)

<table>
<thead>
<tr>
<th></th>
<th>Low Pro</th>
<th>Med Pro</th>
<th>Hi Pro</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Pts</td>
<td>37</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Protein in g/kg/d</td>
<td>0.8 ± 0.3</td>
<td>1.1 ± 0.2*</td>
<td>1.5 ± 0.3*</td>
</tr>
<tr>
<td>Kcal/kg/d</td>
<td>22 ± 7</td>
<td>25 ± 6</td>
<td>27 ± 7*</td>
</tr>
<tr>
<td>E BAL kcal/kg/d</td>
<td>-6 ± 9</td>
<td>-4 ± 6*</td>
<td>-2 ± 7*</td>
</tr>
<tr>
<td>NBAL g/d</td>
<td>-6.6 ± 5.4</td>
<td>-4.6 ± 5.4*</td>
<td>-2.6 ± 7.5*</td>
</tr>
<tr>
<td>ICU LOS, d</td>
<td>5 (3–9)</td>
<td>10 (6–14)*</td>
<td>10 (7–15)*</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>27%</td>
<td>24%</td>
<td>16%</td>
</tr>
</tbody>
</table>


28 d survival of 3 groups (n = 37, 38, 38) based on protein intake (0.8, 1.1, 1.5 g/kg/d)
• Improved survival time but without improved absolute mortality (ICU mortality: 27%, 24%, 16%)
• Authors hypothesized that a higher protein intake improves outcome

Clinical Outcomes Related to Protein Delivery

Mortality odds by protein and energy intake (> 80% prescribed) in ICU for > 4 vs 12 days (N = 4040 from 202 sites; 2828 & 1584, respectively)
Prescribed: 24 kcal/kg/d, 1.2 g/kg/d protein
~2/3 medical patients; 61 yrs of age

Mortality odds by protein and energy intake (≥80% prescribed) in ICU for > 4 vs 12 days (N = 202 sites; 2828 & 1584, respectively)
Prescribed: 24 kcal/kg/d, 1.2 g/kg/d protein
~2/3 medical patients; 61 yrs of age

### Table 2. Mortality Outcomes Relative to Protein and Energy Intake Delivered.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients in ICU ≥4 d: 60-Day Mortality</th>
<th>Patients in ICU ≥12 d: 60-Day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Protein intake (mean daily delivery)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80% of prescribed vs &lt;80%</td>
<td>0.67</td>
<td>0.63</td>
</tr>
<tr>
<td>Energy intake (mean daily delivery)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80% of prescribed vs &lt;80%</td>
<td>0.76</td>
<td>0.73</td>
</tr>
<tr>
<td>&lt;80% vs &lt;80% of prescribed</td>
<td>(0.62, 0.94)</td>
<td>(0.58, 0.91)</td>
</tr>
</tbody>
</table>

CI: confidence interval; ICU: intensive care unit.
*Adjusted for body mass index (BMI), ICU geographic region, sex, admission type, age, available days in the ICU, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score.
*Adjusted for BMI, ICU geographic region, sex, admission type, age, available days in the ICU, APACHE II score, SOFA score, and energy intake.
*Adjusted for BMI, ICU geographic region, sex, admission type, age, available days in the ICU, and APACHE II score, SOFA score, and protein intake.


60d mortality relative to protein intake and NUTRIC risk group. The odds of death decreased by 10% and 6.6% with each 10% increase in protein intake relative to goal for 4 vs 12 day ICU stay.

Similar relationship with caloric intake

NUTRIC score > 5 = high risk
Nutric Scoring System

Clinical Outcomes Related to Protein Delivery

213 adult surgical patients
Mean age 63 yrs; 30% trauma, 28%/17% elective/emergent surgery
Received > 72 hrs of EN (TF + protein suppl)
Initial calorie and protein targets: 25 – 30 kcal/kg/d
and 1.5 – 2.0 g/kg/d
What is the Optimal Protein Intake for Critically Ill Patients?

• ESPEN guidelines (2009):
  1.3 – 1.5 g/kg ideal body weight/d

• SCCM-ASPEN guidelines (2016):
  1.2 – 2 g/kg/d

• NNI International Protein Summit (2017):
  Minimum 1.2 g/kg/d with doses up to 2 – 2.5 g/kg/d

McClave SA et al. JPEN.2016;40:159-211.

Optimal Protein Requirements for Critically Ill Patients

• 18 trauma patients (ISS > 16) and 5 septic patients; examined body composition during EN/PN after pt stable
• Retrospective, not-randomized, mean intake for 10d (EN)
• Protein based on FFM (corrected for overhydration)
• Average corrected weight in grp A was 18 kg > grp C

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Protein (g/kg/day)</th>
<th>Total Body Protein (kg)</th>
<th>Total Body Fat (kg)</th>
<th>Total Body Glycogen (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 0</td>
<td>Day 0</td>
<td>Day 0</td>
</tr>
<tr>
<td>A  (n = 7)</td>
<td>1.14 ± 0.12*</td>
<td>12.8 ± 3.1</td>
<td>10.9 ± 3.1</td>
<td>15.5 ± 6.9</td>
</tr>
<tr>
<td>B  (n = 8)</td>
<td>1.47 ± 0.11*</td>
<td>-1.8 ± 0.8</td>
<td>NS</td>
<td>-0.1 ± 2.1</td>
</tr>
<tr>
<td>C  (n = 8)</td>
<td>1.86 ± 0.14*</td>
<td>-0.8 ± 0.6</td>
<td>10.7 ± 2.2</td>
<td>16.5 ± 8.2</td>
</tr>
<tr>
<td>P &lt; .001</td>
<td></td>
<td>0.06</td>
<td>NS</td>
<td>-6.6 ± 0.8</td>
</tr>
</tbody>
</table>

*Mean ± st.  *P < .001 for all pairwise comparisons
A: *analysis of variance.

Recommended 1.2 g/kg actual body weight/d (1.5 g/kg FFM/d)

What is the Optimal Protein Intake for Critically Ill Patients?


Protein Intake g/kg/d N
1.1 4
1.5 7
2.2 7

6 severely burned (TBSAB 35-85%) adults
Cross-over design
HP = 2.2 g/kg/d
LP = 1.4 g/kg/d
40% increase in protein synthesis
Marked increase in urea production

Critical Illness Induces a Reprioritization of Protein Synthesis

Schematic overview of tissue-specific protein turnover (% per day) in humans

Boirie Y. Cuthbertson Lecture. ESPEN meeting (Barcelona). 2012.

Optimal Protein Intake for Critically Ill Patients according to the 2016 SCCM-ASPEN guidelines

<table>
<thead>
<tr>
<th>Population</th>
<th>Protein Dose - g/kg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critically ill</td>
<td>1.2 to 2</td>
</tr>
<tr>
<td>Traumatic Brain Injury</td>
<td>1.5 to 2.5</td>
</tr>
<tr>
<td>Sepsis (acute phase)</td>
<td>1.2 to 2</td>
</tr>
<tr>
<td>Burns</td>
<td>1.5 to 2</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>AKI 1.2 to 2</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>CRRT up to 2.5</td>
</tr>
<tr>
<td>Hepatic Failure</td>
<td>Avoid restriction</td>
</tr>
<tr>
<td>Obesity</td>
<td>BMI 30 -39.9 2 g/kg IBW/d</td>
</tr>
<tr>
<td></td>
<td>BMI ≥ 40 2.5 g/kg IBW/d</td>
</tr>
</tbody>
</table>

McClave SA et al. JPEN.2016;40:159-211.
Optimal Protein Intake for Critically Ill Patients according to the NNI International Protein Summit

- Minimum of 1.2 g/kg/d up to 2 - 2.5 g/kg/d
- Certain populations that may need higher end of recommended protein dosing range:
  - Trauma
  - Burns
  - Older (age > 60 years)
  - CRRT
  - Obesity


Impact of Protein Intake on NBAL in Septic and Traumatic Stress

9 pts with deep abscess or serious infection. Randomized to receive PN with 1.2 or 2.3 g/kg/d (caloric intake = 1.35 X REE). 3 patients received both. Greig PD et al. Am J Clin Nutr. 1987;46:1040-7.

Are All Critically Ill Patients the Same?

- Improved outcomes with > 1.2, 1.3, 1.5 g/kg/d
- Improved nitrogen balance and increased protein synthesis with increasing protein intake
- Medical vs. Surgical (Elective) vs. Surgical (Emergent) vs. Multiple Trauma vs. Thermal Injury

- 300 observations in 249 trauma ICU patients
- ICU LOS: 24 ± 19 d
- Vent days: 18 ± 25 d
- Mortality: 10%

Mean NBAL (Allingstrup)
- -6.6 g/d @ 0.8 g/kg/d
- -4.6 g/d @ 1.1 g/kg/d
- -2.6 g/d @ 1.5 g/kg/d

A reappraisal of nitrogen requirements for patients with critical illness and trauma

Roland N. Dickerson, PharmD, Stefanie L. Pitts, PharmD, George O. Maibh IB, MD, Thomas J. Schreipper, MD, Louis J. Magnotti, MD, Martin A. Croce, MD, Gayle Minard, MD, and Rex O. Brown, PharmD Memphis, Tennessee

300 observations in 249 trauma ICU patients

TABLE 4. Effect of Protein Intake Upon Achievement of Nitrogen Equilibrium or Positive NB

<table>
<thead>
<tr>
<th>Protein Intake Range, g/kg/d</th>
<th>Protein Intake, mean (SD), g/kg/d</th>
<th>Energy Intake, mean (SD), kcal/kg/d</th>
<th>Serum Urea Nitrogen, mean (SD), mg/dL</th>
<th>NB Studies, n</th>
<th>Nitrogen Equilibrium, n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>0.2 (0.2)</td>
<td>4 (4)</td>
<td>15 (9)</td>
<td>47</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>0.5-0.99</td>
<td>0.7 (0.1)</td>
<td>8 (4)</td>
<td>19 (14)</td>
<td>60</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>1-1.49</td>
<td>1.2 (0.2)</td>
<td>15 (4)</td>
<td>17 (10)</td>
<td>73</td>
<td>21 (29%)</td>
</tr>
<tr>
<td>1.5-1.99</td>
<td>1.7 (0.1)</td>
<td>22 (5)</td>
<td>18 (7)</td>
<td>61</td>
<td>23 (38%)</td>
</tr>
<tr>
<td>2-2.49</td>
<td>2.2 (0.1)</td>
<td>28 (5)</td>
<td>18 (8)</td>
<td>47</td>
<td>23 (49%)</td>
</tr>
<tr>
<td>≥2.5</td>
<td>2.7 (0.2)</td>
<td>33 (6)</td>
<td>23 (16)</td>
<td>12</td>
<td>9 (75%)</td>
</tr>
</tbody>
</table>


Do TBI Patients Need More Protein?

Caloric Contribution of Protein Oxidation to Energy Expenditure

<table>
<thead>
<tr>
<th>Dx</th>
<th>Contribution to REE</th>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI</td>
<td>24 ± 7%</td>
<td>Clifton, 1984</td>
</tr>
<tr>
<td>TBI</td>
<td>30 ± 4%</td>
<td>Dickerson, 1990</td>
</tr>
</tbody>
</table>


Optimal Protein Intake for Critically Ill Patients according to the NNI International Protein Summit

- Minimum of 1.2 g/kg/d up to 2 - 2.5 g/kg/d
- Certain populations that may need higher end of recommended protein dosing range:

  Trauma
  Burns
  Older (age > 60 years)
  CRRT
  Obesity

Protein Requirements in Thermal Injury

- ESPEN (2013): 1.5 to 2 g/kg/d
- SCCM-ASPEN (2016): 1.5 to 2 g/kg/d
- Nestlé Protein Summit: Up to 2 to 2.5 g/kg/d

McClave SA et al. JPEN. 2016;40:159-211.


Six burned adults; Low Protein 1.4 vs. High Protein 2.2 g/kg/d; 1.25 X REE
No signif diff in NET protein dynamics but 40% increase in synthesis

Optimal Protein Intake for Critically Ill Patients according to the NNI International Protein Summit

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• Certain populations that may need higher end of recommended protein dosing range:
  - Trauma
  - Burns
  - Older (age > 60 years)
  - CRRT
  - Obesity


Anabolic Resistance of Aging

Role of dietary protein in the sarcopenia of aging$^{1-4}$

*Douglas Paddon-Jones, Kevin R Short, Wayne W Campbell, Elena Volpi, and Robert R Wolfe*

Insulin resistance of muscle protein metabolism in aging

Blake B. Rasmussen,$^3$† Satoshi Fujita,$^3$ Robert R. Wolfe,$^3$ Beatrice Minnearther,$^3$
Mona Roy,$^3$ Vincent L. Rowe,$^3$ and Elena Volpi$^2$$^4$

Aging, exercise, and muscle protein metabolism

*Rene Koopman$^{1,2}$ and Luc J. C. van Loon$^1$

Frailty amplifies the effects of aging on protein metabolism: role of protein intake$^{1-3}$

*Stephanie Chevalier, Réjeanne Gougeon, Kieran Nayar, and José A Morais*
Protein Requirements May Be Altered For Older Patients

- Protein maintenance 0.8 to 1 g/kg/d in younger patients;
- Protein maintenance 1 to 1.2 g/kg/d for elderly
- ≥ 1.4 g/kg/d for those with decubitus ulcers
- Frail elderly patients may require more (Chevalier S, Am J Clin Nutr. 2003;78:422-9.)

54 older (> 60, mean 71 ± 9 yrs) and 195 younger patients (18-59, mean 37 ± 12 yrs). Trauma ICU; NB: day 4 to 7.
85% fed via EN, 11% PN, 4% both

Dickerson RN et al. JPEN.2015;29:282-90.
**Influence of Aging on Nitrogen Accretion During Critical Illness**

Dickerson RN et al. JPEN. 2015; 29: 282-90.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Older</th>
<th>Younger</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BUN (mg/dL)</strong></td>
<td>23 ± 13</td>
<td>16 ± 9</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Creatinine (mg/dL)</strong></td>
<td>0.9 ± 0.3</td>
<td>0.8 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Measured CrCL(mL/min)</strong></td>
<td>103 ± 40</td>
<td>179 ± 67</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Predicted CrCL(mL/min)</strong></td>
<td>78 ± 29</td>
<td>136 ± 47</td>
<td>0.001</td>
</tr>
</tbody>
</table>

P = NS between slopes via ANCOVA

Optimal Protein Intake for Critically Ill Patients according to the NNI International Protein Summit

- Minimum of 1.2 g/kg/d up to 2 - 2.5 g/kg/d
- Certain populations that may need higher end of recommended protein dosing range:
  - Trauma
  - Burns
  - Older (age > 60 years)
  - CRRT
  - Obesity

Protein Dosing for Patients with Kidney Disease

- ASPEN Guidelines (2010):
  - HD: up to 1.5 g/kg/d
  - CRRT: 1.8 to 2.5 g/kg/d
  - CKD with maintenance HD: 1.2 g/kg/d

- SCCM-ASPEN (2016):
  - AKI: 1.2 to 2 g/kg/d
  - CRRT or frequent HD: increased protein, up to a max of 2.5 g/kg/d

Protein Dosing for Patients with Kidney Disease

- ESPEN (2006 [EN] and 2009 [PN]):
  - HD: 1.2 to 1.4 g/kg/d
  - CRRT: at least 1.5 g/kg/d, max 1.7 g/kg/d
  - CKD without HD: 0.55 to 0.6 g/kg/d
• 50 critically ill, vent-depend pts required CRRT
• 40 received 1.5, 2, 2.5 g/kg/d X 2 d each as an isocaloric diet
• 10 patients randomized to receive 2 g/kg/d X 6d
• Measured REE (2/3 of pop) or Schofield eq.


• NB was NOT time dependent
• Positive NB more likely at ≥ 2 g/kg/d
• Mean NB (died): -4.1 g/d
• Mean NB (survived): +0.2 g/d
• For every 1 g/d increase in NB, the probability of survival improved by 21% (p = 0.03)

Hepatic Failure

- **SCCM-ASPEN Guidelines (2016):**
  Avoid restricting protein in patients with liver failure, using the same recommendations for other critically ill patients.

- **ESPEN Guidelines on PN: Hepatology (2009):**
  Acute or subacute liver failure: 0.8 to 1.2 g/kg/d
  Liver cirrhosis: 1.2 to 1.5 g/kg/d
  Employ blood ammonia to adjust amino acid provision

McClave SA et al. JPEN. 2016;40:159-211.

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**Normal protein diet for episodic hepatic encephalopathy: results of a randomized study**

Juan Córdoba1,2, Juan López-Hellín3, Mercè Planas1, Pilar Sabin1, Francesc Sanpedro1, Francisco-Castel1, Rafael Esteban1, Juana González1

20 evaluable patients with cirrhosis and PSE. Randomized to receive a low protein EN with progressive increments every 3 days to achieve up to 1.2 g/kg/d for last 2 days vs. 1.2 g/kg/d on first day for 14 days.

Authors conclusions: “Diets with normal content of protein can be administered safely to patients with episodic hepatic encephalopathy. Restriction of the content of protein does not appear to have any beneficial effect.”

Optimal Protein Intake for Critically Ill Patients according to the NNI International Protein Summit

- Minimum of 1.2 g/kg/d up to 2 - 2.5 g/kg/d
- Certain populations that may need higher end of recommended protein dosing range:
  - Trauma
  - Burns
  - Older (age > 60 years)
  - CRRT

**Obesity**


Protein Intake in Obesity

- **SCCM-ASPEN guidelines (2016):**
  - BMI 30 to 40 kg/m²: 2 g/kg IBW/d (with 11 to 14 kcal/kg actual wt/d)
  - BMI > 40 kg/m²: 2.5 g/kg IBW/d (with 22 to 25 kcal/kg IBW/d when BMI > 50)

- **ASPEN guidelines (2013):**
  - 1.2 g/kg actual wt/d or 2 to 2.5 g/kg IBW/d (with < 14 kcal/kg actual wt/d) – adjust protein intake based on NBAL
  - ICU patients require 2 to 2.5 g/kg IBW/d
  - Non-ICU patients require 1.8 to 1.9 g/kg IBW/d

McClave SA et al. JPEN.2016;40:159-211.
Obesity Compounds the Metabolic Response to Critical Illness and the Adverse Effects of Overfeeding

- Increased incidence of diabetes mellitus
- Increased incidence of hyperlipidemia
- Decreased VC, TLC, and FRV with morbid obesity; increased difficulty with ventilator weaning
- Decreased LV contractility and EF; LV hypertrophy and increased LVEDP
- Increased incidence of fatty liver

Hospitalized Obese Patients Exhibit Wide Variability in Energy Expenditure

**Can Net Protein Anabolism Be Achieved During Hypocaloric High Protein Nutrition Therapy?**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Design</th>
<th>N</th>
<th>Population</th>
<th>PN or EN</th>
<th>Protein g/kg IBW/d</th>
<th>Kcals in Kcal/kg IBW/d</th>
<th>Mean NBAL g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dickerson, 1986</td>
<td>Prospective</td>
<td>13</td>
<td>Non-ICU PN</td>
<td>PN</td>
<td>2.1</td>
<td>25</td>
<td>+2.4</td>
</tr>
<tr>
<td>Burge, 1994</td>
<td>RCT</td>
<td>9</td>
<td>Non-ICU PN</td>
<td>PN</td>
<td>2.0 (2.2)</td>
<td>14 (22)</td>
<td>+1.3 (2.8)</td>
</tr>
<tr>
<td>Choban, 1997</td>
<td>RCT</td>
<td>16</td>
<td>ICU + Non-ICU</td>
<td>PN</td>
<td>2.0</td>
<td>22 (36)</td>
<td>+4.0 (3.6)</td>
</tr>
<tr>
<td>Choban &amp; Dickerson, 2002</td>
<td>Retrospective</td>
<td>28</td>
<td>Trauma ICU</td>
<td>EN</td>
<td>1.5 (1.8)</td>
<td>22 (30)</td>
<td>-1.4 (-2.7)</td>
</tr>
<tr>
<td>Dickerson, 2002</td>
<td>Retrospective</td>
<td>22</td>
<td>Class 3 vs Class 1 &amp; 2</td>
<td>EN+ PN</td>
<td>See regression analysis (figures)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Outcomes During Hypocaloric High Protein Nutrition Therapy in Obesity**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Design</th>
<th>N</th>
<th>Population</th>
<th>PN or EN</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dickerson, 1986</td>
<td>Prospective</td>
<td>13</td>
<td>Non-ICU PN</td>
<td>PN</td>
<td>Healed wounds, closed fistulae</td>
</tr>
<tr>
<td>Burge, 1994</td>
<td>RCT</td>
<td>9</td>
<td>Non-ICU PN</td>
<td>PN</td>
<td>No diff in morbidity or mortality, serum protein response</td>
</tr>
<tr>
<td>Choban, 1997</td>
<td>RCT</td>
<td>16</td>
<td>ICU + Non-ICU</td>
<td>PN</td>
<td>No diff in morbidity or mortality, required less insulin therapy</td>
</tr>
<tr>
<td>Dickerson, 2002</td>
<td>Retrospective</td>
<td>28</td>
<td>Trauma ICU</td>
<td>EN</td>
<td>Decreased ICU LOS, antibiotic therapy days, and trend in mech vent days; No diff in hosp LOS, mortality</td>
</tr>
<tr>
<td>Choban &amp; Dickerson, 2005</td>
<td>Retrospective</td>
<td>22</td>
<td>Class 3 vs Class 1 &amp; 2 ICU + non</td>
<td>EN+ PN</td>
<td>Trend in worsening hyperglycemia (p =NS)</td>
</tr>
</tbody>
</table>
Impact of Extent of Obesity Upon Nitrogen Balance


Can Net Protein Anabolism Be Achieved in Older Patients During Hypocaloric High Protein Nutrition Therapy?

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Design</th>
<th>N</th>
<th>Population</th>
<th>PN or EN</th>
<th>Protein g/kg IBW/d</th>
<th>Kcals in Kcal/kg IBW/d</th>
<th>Mean NBAL g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu, 2000</td>
<td>Retrospective</td>
<td>18</td>
<td>Younger vs. Older</td>
<td>PN</td>
<td>1.6 Adj</td>
<td>18 Adj</td>
<td>+3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td></td>
<td>1.6 Adj</td>
<td>18 Adj</td>
<td></td>
<td>+0.2*</td>
</tr>
<tr>
<td>Dickerson, 2013</td>
<td>Retrospective</td>
<td>44</td>
<td>Younger vs Old, ICU</td>
<td>PN</td>
<td>1.9</td>
<td>18</td>
<td>-4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33</td>
<td></td>
<td>EN+ PN</td>
<td>2.1</td>
<td>21</td>
<td>-3.2Δ</td>
</tr>
</tbody>
</table>

*At a protein intake of 2.3 g/kg IBW/d for both groups
*p=0.07
### Clinical Outcomes with Hypocaloric High Protein Nutrition Therapy in Older Patients

<table>
<thead>
<tr>
<th>Author, year</th>
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<tr>
<td>Liu, 2000</td>
<td>Retrospective</td>
<td>18</td>
<td>Younger vs. Older</td>
<td>PN</td>
<td>No diff in morbidity or mortality</td>
</tr>
<tr>
<td>Dickerson, 2013</td>
<td>Retrospective</td>
<td>44</td>
<td>Younger vs Older, ICU</td>
<td>EN+ PN</td>
<td>No diff in morbidity, mortality, or LOS; Older patients had a greater risk for developing azotemia (SUN 30 vs. 20 mg/dL, P = 0.001)</td>
</tr>
</tbody>
</table>

\[ \Delta \text{at a protein intake of 2.3 g/kg IBW/d for both groups; } p=0.07 \]

---

No difference in clinical outcomes

Dickerson RN et al. JPEN.2013; 37:342-351.
Adverse Effect of Hypocaloric, Low Protein Nutrition Therapy in Critically Ill Patients with Obesity

<table>
<thead>
<tr>
<th>BMI</th>
<th>N</th>
<th>Kcals/d</th>
<th>Prot g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>289</td>
<td>994</td>
<td>45</td>
</tr>
<tr>
<td>20 - 24.9</td>
<td>937</td>
<td>1024</td>
<td>47</td>
</tr>
<tr>
<td>25 - 29.9</td>
<td>818</td>
<td>1074</td>
<td>47</td>
</tr>
<tr>
<td>30 - 34.9</td>
<td>395</td>
<td>1008</td>
<td>48</td>
</tr>
<tr>
<td>35 - 39.9</td>
<td>162</td>
<td>1009</td>
<td>46</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>171</td>
<td>1048</td>
<td>60</td>
</tr>
</tbody>
</table>


Should Hypocaloric High Protein Therapy be Applied during Early Critical Illness?

- SCCM-ASPEN guidelines (2016):
  \[ \leq 20 \text{ kcal/kg/d or 80\% of estimated energy needs with adequate protein (\geq 1.2 g/kg/d) be considered in high risk or severely malnourished patients over the first week in the ICU.} \]

- NNI International Protein Summit (2017):
  Provision of 80 to 90\% of caloric requirements partnered with protein doses of 1.2 to 2.5 g/kg/d be used in the critically ill patient admitted to the ICU. Energy may be increased to meet requirements as patients recover from the acute phase of critical illness.

McClave SA et al. JPEN.2016;40:159-211.
Should Hypocaloric High Protein Therapy be Applied during Early Critical Illness?

- Data to support this concept are limited
- Probably done more often than not in clinical practice due to:
  1. restriction of carbohydrate intake due to hyperglycemia
  2. restriction of total kcals: hypercapnia
  3. provision of exogenous kcals (e.g. propofol)
  4. gastric feeding intolerance in high risk populations (e.g., TBI ~20%)

Clinical Outcomes Related to Protein and Calorie Delivery

Data extracted by: Heyland DK. JPEN.2017;40:156-158.
High-protein hypocaloric vs normocaloric enteral nutrition in critically ill patients: A randomized clinical trial
Saulí Rugeles, MD, Luis Gabriel Villarraga-Angulo, MD, Aníbal Arina-Gutiérrez, MD, Santiago Chaverra-Kornerup, MD, Pieralesandro Lazalva, Diego Rosselli, MD, MSC, MEd SA

- RCT, ICU patients (mostly medical), 54 vs. 52 yrs of age
- EN + protein supplements for ≥ 4 d; Study duration: 7 d
- Goals: 15 vs. 25 kcal/kg/d + 1.7 g/kg/d protein for both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypocaloric</th>
<th>Eucaloric</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td>13.5 ± 6.4</td>
<td>13.7 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Start EN, ICU day</td>
<td>2.0 ± 2.2</td>
<td>2.1 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Kcals/d at 48h</td>
<td>13 ± 3</td>
<td>21 ± 5</td>
<td>0.001</td>
</tr>
<tr>
<td>Protein g/d at 48h</td>
<td>1.4 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>∆ SOFA</td>
<td>-0.8 ± 3.1</td>
<td>-1.0 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>28d Mortality</td>
<td>30%</td>
<td>27%</td>
<td>NS</td>
</tr>
<tr>
<td>Pts require RHI, n</td>
<td>15 (25%)</td>
<td>27 (45%)</td>
<td>0.022</td>
</tr>
<tr>
<td>IU/d (96 h)</td>
<td>0 ± 0.3</td>
<td>0 ± 14.3</td>
<td>0.027</td>
</tr>
</tbody>
</table>


What is the Maximum Dose of Protein that can be Safely Given?

Appropriate protein provision in critical illness: a systematic and narrative review1-3
L. John Hoffer and Bruce R Bistrian

“The prevalent opinion that 1.2 to 1.5 g/kg/d is sufficient in critical illness [e.g., ESPEN] appears to be based on the biased selection of small and unrepresentative subset of low quality studies that enrolled critically ill, energy-overfed patients.”

“...doses between 2.5 and 3 g/kg/d are safe for use... except in patients with refractory hypotension, overwhelming sepsis or serious liver disease.”

Markers of Protein Intake Adequacy and Recovery

- Nitrogen Balance – hard to do, often over-estimated, unreliable without nursing education and if not adequately emphasized
- Serum Protein Response (e.g., prealbumin – negatively sensitive to stress, infection, and inflammation)
- Clinical Response (not easily measurable)

Summary

- Critically ill patients should receive at least 1.2 g/kg/d of protein and often require 1.5 to 2.5 g/kg/d.
- Protein intake should be adjusted for disease condition and concurrent energy intake.
- Protein intake may be titrated according to nitrogen balance.
- Achievement of adequate protein intake is more important than caloric intake during critical illness.
Nitrogen Balance
The “Gold Standard” for Clinical Practice

• Only reflects the net difference between nitrogen intake and nitrogen loss
• Is often overestimated due to inadequate urine collection or additional losses
• Does not reveal information regarding nitrogen distribution, synthesis, catabolism among tissues and organs.
The “Classic” Nitrogen Balance Technique

• A patient who exhibits a:
  • nitrogen balance of +4 to +6 g/day is considered reflective of protein anabolism
  • nitrogen balance of -4 to +4 g/day is considered to be in nitrogen equilibrium
  • Nitrogen balance worse than -4 to -5 g/day is considered to be catabolic

The “Classic” Nitrogen Balance Technique

• Collect 24 hr urine for urea nitrogen
• NBAL (g/d) = Nitrogen in – Nitrogen out
• Nitrogen in (g/d) = Protein (g/d)/6.25
• Nitrogen out = urinary urea nitrogen + 4 g
• 4 g = account for skin/stool (2 g) + non-urea nitrogen in the urine (2 g)
• NBAL (g/d) = Nit in (g/d) – UUN (g/d) – 4
### Total Urinary Nitrogen Excretion: A Marker of Catabolism

- 10 to 12 g/d Normal*
- 12 to 15 g/d Mild Stress (Post op)
- 15 to 20 g/d Moderate Stress
- > 20 g/d Severe Stress

* After an overnight fast or while not receiving specialized nutrition support

### Non-Urea Urinary Nitrogen, Stool, and Insensible Nitrogen Losses

- 564 urine samples from 81 surgical patients (day 1 to 38) and healthy obese/non-obese subjects
- TUN-UUN = 1.8 + 0.9 g/d
- 103 stool samples from 10 patients (unpublished results): 1.2 + 0.8 g/d
- Estimate of 0.5 g N/d for insensible losses (Calloway DH et al. J Nutr.1971;101:775-86).

• 55 trauma ICU patients receiving SNS
• NBAL @ 4.4 ± 2.6 d
• TUN-UUN = 3.8 ± 2.8 g/d
• Evaluated 8 different methods for estimating non-urea nitrogen
• UUN/0.85 most precise


### Correction Factors for Total Nitrogen Excretion (g/d)*

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Non-UUN</th>
<th>Drainage N</th>
<th>Diarrhea N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals</td>
<td>37</td>
<td>1.3 ± 0.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Depleted</td>
<td>67</td>
<td>1.6 ± 0.8</td>
<td>0.8 ± 0.6</td>
<td>3.0 ± 1.6</td>
</tr>
<tr>
<td>Post-Operative</td>
<td>96</td>
<td>2.0 ± 1.2</td>
<td>1.4 ± 1.1</td>
<td>2.7 ± 0.8</td>
</tr>
<tr>
<td>Injured</td>
<td>43</td>
<td>2.8 ± 1.3</td>
<td>1.0 ± 1.0</td>
<td>2.5 ± 0.9</td>
</tr>
<tr>
<td>Septic</td>
<td>31</td>
<td>3.1 ± 1.7</td>
<td>1.0 ± 0.7</td>
<td>2.6 ± 1.6</td>
</tr>
<tr>
<td>average</td>
<td></td>
<td>1.1 ± 0.9</td>
<td>2.7 ± 1.4</td>
<td></td>
</tr>
</tbody>
</table>

*Data expressed as mean ± SD from 260 adult patients + 37 control subjects

Body Urea Nitrogen Appearance  
(For Patients with Renal Insufficiency)  
Not necessary in clinical practice unless a BUN change > 5 mg/dL over the NBAL determination

Body Urea (g/d) = \(TBW(L) \times (\text{BUN}_f - \text{BUN}_i) \times 0.01\)

Total Body Water = 0.55 L/kg (female) 
0.60 L/kg (male)

\[\text{NBAL} = \text{Nin} - \frac{\text{UUN}}{0.85} - \text{Body Urea} - 2^*\]

*If without diarrhea or other drainage losses


Measured Creatinine Clearance as a Marker of Adequacy of Urinary Collection

• Measured Creatinine Clearance should be ± 20% for non-critically ill patients

• ≥ 90% of predicted (by the Cockroft-Gault equations) for critically ill patients

Table 3. Nt, Creatinine Clearance, and Predicted Creatinine Clearance

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>With T</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>249</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Urine creatinine, mean (SD), mg/d</td>
<td>1,842 (678)</td>
<td>1,861 (6)</td>
<td></td>
</tr>
<tr>
<td>Measured CrCl, mean (SD), mL/min</td>
<td>164 (68)*</td>
<td>174 (6)</td>
<td></td>
</tr>
<tr>
<td>Predicted CrCl, mean (SD), mL/min</td>
<td>126 (46)</td>
<td>136 (4)</td>
<td></td>
</tr>
</tbody>
</table>