4.2c Composition of Enteral Nutrition: High Protein vs. Low Protein

**Question:** Compared to a lower enteral protein intake does a higher protein intake enteral formula result in better outcomes in the critically ill adult patient?

**Summary of evidence:** There were 3 level 2 studies that compared the effect of a higher protein regimen to a lower protein regimen. Clifton (1985) compared the high-protein formula Traumacal to the lower protein formula Magnacal in head injured patients. Rugeles (2014) compared a hypocaloric hyperprotein regimen to a standard regimen. Fetterplace (2018) compared the high protein formula Nutrison Protein Plus to the lower protein formula Nutrison in medical and surgical ICU patients. Scheinkestel (2003) was excluded from this review because the average protein goals of the two groups did not differ (the control group’s protein goal was 2 g/kg/d vs the intervention group’s protein goal was 1.5 g/kg/d x 2 days, 2.0 g/kg/d x 2 days and 2.5 g/kg/d x 2 days).

**Mortality:** All three studies reported on mortality, though at different time intervals. Overall, there was no effect on mortality (RR 0.89, 95% CI 0.50, 1.60, p=0.70, I² heterogeneity=0%; figure 1).

**Infections:** In the study that reported on infections (Clifton, 1985), there were more bacterial infections in the group receiving the higher protein formula but this was not statistically significant (RR 1.50, 95% CI 0.32, 7.1).

**LOS and Ventilator days:** Two studies reported on these outcomes (Rugeles 2014, Fetterplace 2018) and there was no significant difference on ICU LOS (WMD -0.94, 95% CI -2.75, 0.87, p=0.31, I² heterogeneity=0%; figure 2), hospital LOS (WMD 3.05, 95% CI -6.24, 12.35, p=0.52, I² heterogeneity=81%; figure 3) or length of mechanical ventilation (WMD -0.02, 95% CI -2.81, 2.77, p=0.99, I² heterogeneity=54%; figure 4).

**Physical Outcomes:** Fetterplace 2018 was the only study that reported on physical outcomes. They found no difference between groups with regards to hand grip strength, muscle strength (Medical Research Council (MRC) scale), ICU acquired weakness (MRC < 48), and physical function (Physical Function in Intensive Care Unit Test (PFIT-s)).

**Other:** In the study by Clifton (1985), nitrogen balance was higher in the higher protein group but this was not statistically significant. Rugeles 2014 showed no difference in calories received but a significant difference in protein received (1.4 g/kg/d vs 0.76 g/kg/d, p <0.0001). Fetterplace 2018 showed significantly higher calories and protein received in the high protein group (84% vs 73% caloric adequacy, p=0.01 and 90% vs 57% protein adequacy, p<0.001). Time to start EN was significantly shorter in the high protein group (13 vs 20 hours, p=0.01). In the high vs low protein groups, there were no differences in diarrhea occurrence (16/30 patients in both groups, p=1.0) and feeding intolerance (30% vs 27%, p=0.77). No difference
was found in the physical outcomes tested, except in quadriceps muscle layer thickness (QMLT) assessed by ultrasound at baseline and ICU discharge. The intervention was associated with less QMLT loss at discharge, with an average attenuated loss of 0.22 cm (95% CI 0.06, 0.38, p=0.01; table 2).

**Conclusions:**

1) A higher protein formula has no effect on mortality in critically ill patients.
2) A higher protein formula has no effect on infectious complications in critically ill head injured patients.
3) A higher protein formula has no effect on ICU length of stay, hospital length of stay or duration of mechanical ventilation in critically ill patients.

**Level 1 study:** if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.

**Level 2 study:** If any one of the above characteristics are unfulfilled.
Table 1. Randomized Studies Evaluating Higher Protein vs. Low Protein Enteral Formula in Critically Ill Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Methods (score)</th>
<th>Intervention</th>
<th>Mortality # (%)</th>
<th>Infections # (%)</th>
<th>RR (CI)**</th>
<th>RR (CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Clifton 1985</td>
<td>Head injured patients</td>
<td>C.Random: not sure</td>
<td>22% pro, 38% CHO, 41% fat, 1.5 Kcal/ml (Traumacal) vs. 14% pro, 50% CHO, 36% fat, 2.0 Kcal/ml (Magnacal)</td>
<td>3 Month 1/10 (10)</td>
<td>3 Month 1/10 (10)</td>
<td>1.00</td>
<td>(0.07-13.9)</td>
</tr>
<tr>
<td></td>
<td>Comatose for 24 hrs</td>
<td>ITT: yes</td>
<td>Isocaloric, 29 gm Nitrogen vs. 17.6 gms Nitrogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=20</td>
<td>Blinding: no</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Rugeles 2013</td>
<td>Medical adult ICU patients</td>
<td>C.Random: no</td>
<td>hypocaloric hyperproteic (15 kcal/kg, 1.7 g/kg x 7 days vs standard (25 kcal/kg, 20% calories from protein).</td>
<td>28 day 11/40</td>
<td>28 day 12/40</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>N=80</td>
<td>ITT: no</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blinding: double</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4) Fetterplace 2018</td>
<td>Medical and surgical ICU</td>
<td>C.Random: yes</td>
<td>1.5 g/kg x 15 days from high protein EN (Nutrison Protein Plus) vs 1.0 g/kg x 15 days from standard EN (Nutrison)</td>
<td>28 day 4/30</td>
<td>28 day 5/30</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>patients. Single centre.</td>
<td>ITT: yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=60</td>
<td>Blinding: single</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

C.Random: concealed randomization  ±: mean ± standard deviation
### Table 1. Randomized Studies Evaluating Higher Protein vs. Low Protein Enteral Formula in Critically Ill Patients (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Mechanical Ventilation</th>
<th>LOS</th>
<th>Nutrition parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High protein</td>
<td>Low Protein</td>
<td>Calories (kcal/kg/d)</td>
</tr>
<tr>
<td></td>
<td>High protein</td>
<td>Low Protein</td>
<td></td>
</tr>
<tr>
<td>1) Clifton 1985</td>
<td>NR</td>
<td>NR</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>2) Rugeles 2013</td>
<td>8.5 ± 4.6 days (40)</td>
<td>9.7 ± 4.9 days (40)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>ICU</td>
<td>Hospital</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>10.4 ± 5.0 days</td>
<td>19.5 ± 6.5 days</td>
<td>21 ± 5.2</td>
</tr>
<tr>
<td></td>
<td>10.6 ± 8.3 days</td>
<td>18.8 ± 10.9 days</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>84 ± 21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>90 ± 25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13 ± 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16/30 (53%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9/30 (30)</td>
</tr>
<tr>
<td>3) Fetterplace 2018</td>
<td>8.7 ± 7.5 days (30)</td>
<td>7.0 ± 5.0 days (30)</td>
<td>27.4 ± 19.0 days</td>
</tr>
</tbody>
</table>

**ITT**: intent to treat  
NR: Not reported  
**RR**: relative risk  
CI: Confidence intervals
Table 2. Physical Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Physical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High protein</td>
</tr>
<tr>
<td></td>
<td>Low Protein</td>
</tr>
<tr>
<td></td>
<td>Handgrip strength, kg</td>
</tr>
<tr>
<td></td>
<td>20 (6.1), n=6</td>
</tr>
<tr>
<td>Muscle strength (MRC score)</td>
<td>55 (5.9), n=7</td>
</tr>
<tr>
<td>ICU acquired weakness (MRC&lt;48)</td>
<td>1 (14), n=7</td>
</tr>
<tr>
<td>Physical function in ICU test</td>
<td>6.8 (3.8), n=8</td>
</tr>
<tr>
<td>Quadriceps Muscle Layer Thickness (ultrasound)</td>
<td>Intervention: effect 0.22, 95% CI 0.06-0.38, p=0.01n=24 (intervention), n=23 (control)</td>
</tr>
</tbody>
</table>
**Figure 1. Mortality**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High Dose</th>
<th>Low Dose</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clifton 1986</td>
<td>1</td>
<td>1</td>
<td>5.0%</td>
<td>1.00 [0.07, 13.87]</td>
<td>1985</td>
</tr>
<tr>
<td>Rugeles 2013</td>
<td>11</td>
<td>12</td>
<td>71.8%</td>
<td>0.92 [0.46, 1.83]</td>
<td>2013</td>
</tr>
<tr>
<td>Fetterplace 2018</td>
<td>4</td>
<td>5</td>
<td>23.3%</td>
<td>0.80 [0.24, 2.69]</td>
<td>2018</td>
</tr>
</tbody>
</table>

Total (95% CI): 80 80 100.0% 0.89 [0.50, 1.60]

Total events: 16 18

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.04$, $df = 2$ ($P = 0.98$); $I^2 = 0$

Test for overall effect: $Z = 0.38$ ($P = 0.70$)

**Figure 2. ICU LOS**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High Dose</th>
<th>Low Dose</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rugeles 2013</td>
<td>9.5</td>
<td>10.4</td>
<td>81.9%</td>
<td>-0.90 [-3.20, 1.40]</td>
<td>2013</td>
</tr>
<tr>
<td>Fetterplace 2018</td>
<td>19.5</td>
<td>20.5</td>
<td>38.1%</td>
<td>-1.00 [-3.93, 1.93]</td>
<td>2018</td>
</tr>
</tbody>
</table>

Total (95% CI): 70 70 100.0% -0.94 [-2.75, 0.87]

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.00$, $df = 1$ ($P = 0.96$); $I^2 = 0$

Test for overall effect: $Z = 1.01$ ($P = 0.31$)

**Figure 3. Hospital LOS**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High Dose</th>
<th>Low Dose</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rugeles 2013</td>
<td>19.5</td>
<td>20.5</td>
<td>57.8%</td>
<td>-1.00 [-3.54, 1.54]</td>
<td>2013</td>
</tr>
<tr>
<td>Fetterplace 2010</td>
<td>27.4</td>
<td>19.0</td>
<td>42.2%</td>
<td>0.60 [0.76, 16.44]</td>
<td>2010</td>
</tr>
</tbody>
</table>

Total (95% CI): 70 70 100.0% 3.05 [-6.24, 12.35]

Heterogeneity: $\tau^2 = 37.24$, $\chi^2 = 5.21$, $df = 1$ ($P = 0.02$); $I^2 = 81$

Test for overall effect: $Z = 0.64$ ($P = 0.52$)
Figure 4. Duration of Ventilation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High Dose</th>
<th>Low Dose</th>
<th>Mean Difference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Ruglesi 2013</td>
<td>8.5</td>
<td>4.8</td>
<td>40</td>
<td>9.7</td>
</tr>
<tr>
<td>Fettweisacco 2018</td>
<td>8.7</td>
<td>7.5</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>70</td>
<td>70</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $Tau^2 = 2.29; Chi^2 = 2.19; df = 1; I^2 = 30%$; $P = 0.54$
Test for overall effect: $Z = 0.02 (P = 0.99)$

Table 3. Excluded Articles

<table>
<thead>
<tr>
<th>#</th>
<th>Reason excluded</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Not high vs low protein - one group received 2/g/kg/d x 6 days. Other group received 1.5 g/kg/d x 2d, 2.0 g/kg/d x 2d, 2.5 g/kg/d x 2d.</td>
<td>Scheinkestel CD, Kar L, Marshall K, Bailey M, Davies A, Nyulasi I, Tuxen DV. Prospective randomized trial to assess caloric and protein needs of critically Ill, anuric, ventilated patients requiring continuous renal replacement therapy. Nutrition. 2003 Nov-Dec;19(11-12):909-16.</td>
</tr>
<tr>
<td>Page</td>
<td>Description</td>
<td>Reference</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>9</td>
<td>Not critically ill patients, not clinically significant outcomes</td>
<td>Tavenier J, Haupt TH, Andersen AL, Buhl SF, Langkilde A, Andersen JR, Jensen JB, Pedersen MM, Petersen J, Andersen O. A high-protein diet during hospitalization is associated with an accelerated decrease in soluble urokinase plasminogen activator receptor levels in acutely ill elderly medical patients with SIRS. Nutr Res. 2017 May;41:56-64.</td>
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</tbody>
</table>