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## Should We Have Equipoise (or Clinical Uncertainty) About How Much Protein to Provide to Critically ill Patients?

One of the most important questions in the critical care nutrition community right now is whether a higher protein dose translates into an improvement in clinical outcomes, as compared to lower protein intake.<sup>1</sup> The 2016 ASPEN/SCCM guideline recommends a wide range of acceptable protein prescription targets (1.2-2.0 grams/kg/day and higher in some select patients) and acknowledge that the underlying evidence for this recommendation is weak.<sup>2</sup> Despite the recommendation, the amount of protein that is actually delivered worldwide ranges widely between 0.5 to 3.8 grams/kg/day (average of 1.3 grams/kg/day).<sup>3</sup> We surmise a wide range in actual protein delivery exists because a weak evidentiary base informs guideline recommendations, and hence, clinical practice.

Accordingly, in partnership with ASPEN, we designed a large, multicenter, pragmatic, volunteer-driven, registry-based, randomized clinical trial of 4000 nutritionally high-risk critically ill patients who will be randomly allocated to a higher dose of protein (>2.2 grams/kg/day) or usual care (<1.2 grams/kg/day), known as the EFFORT trial (see [www.criticalcarenutrition.com](http://www.criticalcarenutrition.com) or [www.nutritioncare.org](http://www.nutritioncare.org) for more information).<sup>4</sup> By setting this target in the higher protein dose, we are ensuring the likelihood of a clear separation of groups, with respect to their protein intake, and yet still within the range of what has been observed, recommended, and used in other research protocols.



To participate in the EFFORT trial, clinicians must concur that clinical equipoise exists regarding optimal critical care nutrition protein dose. Clinical equipoise stipulates an RCT is only ethical insofar as there exists, at the outset, a state of genuine uncertainty amongst medical experts about the therapeutic benefits of each arm of the study. In other words, clinicians must acknowledge that both protein dosing strategies are safe and may be efficacious. However, practitioners who believe that either the high or low dose is harmful will decline participation in the RCT. We contend clinical equipoise exists and the purpose of this brief narrative review is to summarize the available evidence that supports our uncertainty about the correct protein prescription for critically ill adults (see Table 1).

### **Evidence Supporting Higher Protein Dose**

- For the most part, mechanistic studies support the assertion that infused amino acids stimulate de novo protein synthesis, result in greater whole body protein balance, and higher doses result in more positive nitrogen balance.<sup>5,6</sup>
- In a double blind single center RCT (n=80) comparing high protein hypocaloric enteral diet to isocaloric enteral diet, the high protein hypocaloric group received significantly more protein (1.4 vs 0.76 g/kg, P ≤ 0.0001), with improved SOFA score at 48 hours and fewer hyperglycemic episodes.<sup>7</sup> However, in this small, underpowered study, there were no differences in other clinically important outcomes.
- In a single center RCT (n=119), medical/surgical ICU patients were randomized to PN providing protein at 0.8 or 1.2 g/kg/day. The group receiving 1.2 g/kg/day had significant improvement in muscle mass and a trend towards increased handgrip strength.<sup>8</sup> However, the actual difference in protein intake between the 2 groups was marginal (0.9 vs. 1.1 grams/kg/day) and it is hard to understand how such a small difference in intake could result in major changes to muscle mass and strength.
- In analyses of large, multicenter, multinational observational databases (n>7000), an additional 30 grams of protein per day or 1000 calories per day during the first 12 days of ICU stay received by patients was associated with reduced infectious complications, shorter mechanical ventilation, improved short-term physical recovery, and reduced mortality.<sup>9,10,11,12</sup> In another observational database analysis (n=2828)<sup>13</sup>,





delivery of > 80% of protein requirements was associated with reduced 60-day mortality (odds ratio [OR] 0.68, and 95% confidence interval [CI]: 0.50, 0.91) but achieving >80% energy requirements was not (OR = 0.92 (0.65-1.30)). Whilst the inferences from these observational analyses are weaker than from RCTs, they are consistent with other single center observational studies that show an association between protein optimization and survival, but a negative or absent effect of caloric intake.<sup>14,15</sup>

- After extensive review of the literature to assess the safety of high dose protein/amino acid administration recently, experts concluded that doses up to 2.5 grams/kg/day are safe, except perhaps in patients with refractory hypotension (which causes hypoperfusion of the liver) and serious liver disease.<sup>16</sup> They acknowledge that high dose protein is associated with or may cause elevated urea levels but the risk or harm associated with isolated high urea levels is unknown.

### **Evidence Against Higher Protein Dose**



- In the Nephroprotect study, a multi-center RCT (n=474) comparing the provision of IV amino acids (IVAA) at a dose of up to 2.0g/kg/day to standard care, the primary outcome of duration of renal dysfunction was not different, nor were tertiary outcomes of mortality, length of stay and quality of life measures.<sup>17</sup> This study represents the strongest evidence against a higher protein dose and suggests that a dose up to 2.0 grams/kg/day will not improve outcomes in a heterogeneous group of ICU patients. Since no two ICU patients are alike, we urge cautious application of these results to nutritionally high-risk patients (such as those studied in the EFFORT trial)<sup>18</sup>, who may benefit from higher protein dose.
- Four observational studies have reported adverse patient outcomes associated with higher protein intake. First, in a single-center cohort study (n=63), increased protein delivery (mean 0.67 g/kg/day) during the first 10 days of ICU stay was associated with increased muscle wasting.<sup>19</sup> Second, in a post-hoc analysis of the multi-center EPaNIC trial (n=4640)<sup>20</sup>, increased protein intake during the first 3 days was associated with lower likelihood of early ICU discharge.<sup>21</sup> Third, in a post-hoc analysis of a single-center RCT (n=66) comparing aggressive nutritional intake to usual care, greater protein received in the first week was associated with significantly increased mortality but protein provided after the first week seemed protective.<sup>22</sup> Fourth, in a single-center, retrospective study (n=455) which categorized protein intake into 3 groups, protein administered at > 0.8 g/kg/day before day 3 was associated with greater mortality than similar intake provided later.<sup>23</sup> These observations suggest potential harm associated with increased protein, particularly in the acute phase of illness, but should be considered hypothesis-generating observations. Nevertheless, they contribute to the uncertainty about the role of protein in critical illness.
- There are pre-clinical and clinical data that suggest protein/amino acids can suppress autophagy and fail to reduce endogenous catabolism in critical illness.<sup>24</sup> The clinical implications of these findings remain to be determined.

### ***Outcomes in renal failure:***

- Nephroprotect was a multicenter RCT comparing provision of IVAA at a dose of up to 2.0g/kg/day to standard care. As stated earlier, this study represents the strongest evidence against a higher protein dose. The rationale of the Nephroprotect study was built on the following observations:
  - Animal models have demonstrated that an increase in renal blood flow in response to a short-term amino acid infusion can protect the kidney from acute ischemic insults.<sup>25</sup>
  - Several observational studies and one RCT document improved nitrogen balance in dialysis patients receiving higher amounts of amino acids.<sup>26,27,28,29,30</sup>
  - A single center RCT (n=53) in critically ill patients demonstrated that a short-term infusion of IVAA led to faster recovery from severe acute renal failure, particularly in those with oliguric renal failure, in those who received dialysis, and in those who developed sepsis.<sup>31</sup>
  - Another single center trial (n=14) compared 2 doses of IVAA in critically ill patients with non-oliguric renal failure (creatinine clearance below 50 mL/min), and those receiving a higher AA dose were more likely to preserve the effect of diuresis and required less furosemide to achieve negative fluid balance.<sup>32</sup>
  - A subgroup analysis of a cluster RCT of 27 ICUs evaluating nutrition guidelines identified 242 critically ill patients at high risk of renal dysfunction at study entry and found those with greater protein dose were less likely to require RRT.<sup>33,34</sup>



- A post-hoc, hypothesis-generating, subgroup analysis of the same trial suggested a survival advantage to those patients with normal renal function who received the supplementary IVAA compared to usual care (21/179 [11.7%] vs. 37/189 [19.6%]), but also suggested potential harm (lower survival) in those with renal dysfunction at baseline (17/60 [28.3%] vs. 7/46 [15.2%]).<sup>35</sup> The later observation was not significant in the adjusted analysis (covariate-adjusted risk difference, -0.6%; 95% CI, -16.2 to 15.2; p = 0.95). However, we note several limitations to this post hoc analysis: 1) Subgroup numbers are small and event rates low, so results are unstable or fragile; 2) There is inconsistency among study outcomes (only mortality showed a significant difference between groups; but quality of life and physical function measures tended to be worse with treatment); and 3) Given the underlying rationale for the Nephroprotect study, that IV AA were intended to improve the outcome of patients with renal dysfunction, there is a lack of compelling biological plausibility for this sub-group finding. Nevertheless, it remains a published hypothesis that IVAA supplementation may increase harm in patients with renal failure (or may save lives in patient with normal kidney function).

## CONCLUSION

Is the critical care nutrition community trapped in a state of clinical equipoise for optimal protein dose? Here, we have presented studies demonstrating the benefits and perils of both high and low protein dose. In other words, we have presented data to suggest: 1) a higher protein dose is better than a lower protein dose; 2) A lower protein dose is better than a higher protein dose; and 3) A lower protein dose is no better or worse than a higher one. Clinicians have no good basis for choosing between two protein dose options, therefore suggesting clinical equipoise. While numerous data points contribute to our understanding of the optimal dose of protein required in critical illness, they were not equally rigorous in study design. We should be cautious about over-interpreting single center trials, observational studies, post-hoc analyses, expert opinion, small trials, trials where protein dose is not the intervention, and those with weak clinical outcomes. All studies included a heterogeneous population of critically ill adult patients. Identifying which critically ill patients will benefit the most from protein is paramount. Clearly, definitive proof from prospective RCTs evaluating different levels of protein intake in nutritionally high-risk patients remains lacking at this time.



The EFFORT trial will help to resolve this controversy if clinicians embrace the uncertainty of the current evidence and enroll their patients. The EFFORT trial is a registry-based, pragmatic RCT situated in real practice. Hence, the results will be very generalizable. The sample size is large (n=4000) so as to detect even a small treatment effect. The focus is on recruiting nutritionally high-risk patients; the sub-populations that are expected to benefit the most from a higher protein intake. And finally, with the dosing strategies used, the EFFORT trial is designed to create adequate separation of the protein intake of the 2 groups and avoid this criticism of prior trials.<sup>8</sup> When available, the results of the EFFORT trial will enhance confidence as to the optimal dose of protein for critically ill patients. In the meantime, we surmise clinicians are indeed trapped in a state of clinical equipoise and are left to follow the best available advice as published in the recent guidelines (start EN early and prescribe from 1.2-2.0 grams/kg/day or higher in some subgroups).

**To learn more about the EFFORT trial or to get your ICU involved, visit [www.criticalcarenutrition.com](http://www.criticalcarenutrition.com)**

The screenshot shows the website for Critical Care Nutrition. The navigation bar includes links for About Us, PEPuP, CPGs, EFFORT/INS, Research, and Resources. A dropdown menu is open under the EFFORT/INS link, showing options for EFFORT, INS: Tools, INS: Best of the Best, and INS: Past Surveys. At the bottom of the page, there is a banner for 'THE EFFORT TRIAL PRESENTED AT ASPEN' with a video recording link and a note about presenting the study at the recent ASPEN Nutrition Science & Practice Conference.

**Table 1. What does the evidence say about protein dose in critically ill patients?**

	Evidence for a Higher Dose	Evidence for a Lower Dose	Equivocal Evidence
<b>Meta-analysis of RCTs</b>			<ul style="list-style-type: none"> <li>5 RCTs comparing higher to lower protein intake showing no difference in mortality.<sup>36</sup> (***)</li> </ul>
<b>RCTs</b>	<ul style="list-style-type: none"> <li>Single center trials demonstrating positive effects on surrogate outcomes.<sup>7,8</sup> (*)</li> </ul>		<ul style="list-style-type: none"> <li>Nephroprotect Trial showing no effect of 1.0 g/kg/day extra IV amino acids.<sup>17</sup> (***)</li> </ul>
<b>Observational</b>	<ul style="list-style-type: none"> <li>Observational analyses showing more protein in early phase associated with better outcomes. (mortality, infections and functional recovery).<sup>11,12,13,14,15,14,15</sup> (**)</li> <li>Post-hoc analysis of Nephroprotect suggesting benefit in patients with normal kidney function.<sup>35</sup> (*)</li> </ul>	<ul style="list-style-type: none"> <li>Post hoc analysis of RCTs and observational study suggesting increased harm with more protein (slower time to discharge, increase muscle mass, increased mortality).<sup>19,21,22</sup> (*)</li> <li>Retrospective analysis of single institutional database suggesting better outcomes with low level of protein (&lt;0.8 g/kg/day) in the first days followed by &gt;1.2 g/kg/day after day 3.<sup>23</sup> (*)</li> </ul>	
<b>Expert opinion</b>	<ul style="list-style-type: none"> <li>ASPEN/SCCM guidelines recommend higher doses in obesity, burns, trauma, and renal failure requiring renal replacement therapy.<sup>2</sup></li> <li>Experts saying higher doses are safe and possibly efficacious.<sup>16</sup></li> </ul>	<ul style="list-style-type: none"> <li>Experts recommending withholding nutrition or limiting intake to minimal amounts during the first week.<sup>37</sup></li> </ul>	
<b>Mechanistic</b>	<ul style="list-style-type: none"> <li>Tracer and nitrogen balance studies showing increased protein/aa associated with more positive whole body protein balance.<sup>5,6</sup></li> <li>Data that supports IV aa improves renal function or renal blood flow.<sup>25</sup></li> <li>Data from patients requiring CRRT suggesting that patients receiving higher doses of protein have a better nitrogen balance.<sup>26-30</sup></li> </ul>	<ul style="list-style-type: none"> <li>Animal data suggesting that IV aa suppress autophagy and fails to suppress endogenous catabolism.<sup>24</sup></li> </ul>	

Legend: \*-weak evidence; \*\* moderate evidence; \*\*\* stronger evidence

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