

# Optimal Protein Provision in Critical Illness



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Protein plays a major role in muscle function and repair, immunity and enzyme production.<sup>1</sup> The large cost to muscle mass during critical illness, with an increase in protein turnover and net protein loss are well understood. This is a review of protein requirements in critical illness and the ability to meet these on the intensive care unit (ICU).

## Introduction

Catabolism is common in patients with critical illness<sup>1</sup> due to the inflammatory response following systemic infection or severe tissue injury. When catabolism drives protein breakdown there is a rapid release of amino acids to enable protein synthesis, however, this is not without cost elsewhere. Muscle protein loss is greater than the rate of protein synthesis, resulting in negative nitrogen balance.<sup>2</sup> The main goal for protein intake is to optimise the acute phase response in terms of immunity and wound healing while protecting skeletal muscle mass and function.<sup>3</sup> In the healthy adult population, protein is recommended at 0.83 g/kg/body weight,<sup>4</sup> in the healthy older adult population this increases to 1-1.2 g/kg/body weight.<sup>5</sup> Critical care guidelines suggest a protein intake between 1.2-2.0 g/kg/d.<sup>6, 7, 8</sup> Within the wide range of current guidelines there is little consensus regarding the optimal protein intake for individual patients.

This article will review the evidence to determine protein requirements in critical illness, discussing whether and how they can be met.

## Protein requirements

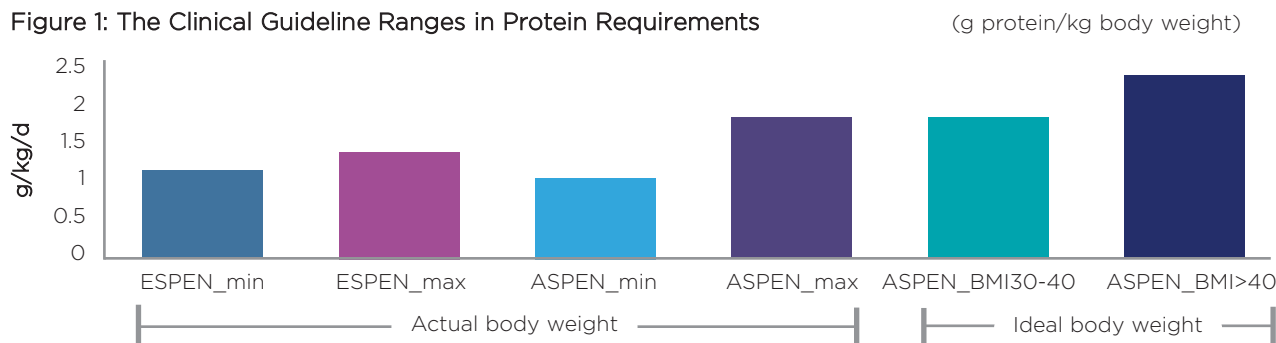
The European Society of Parenteral and Enteral Nutrition (ESPEN) suggest 1.3-1.5 g/kg/day.<sup>8</sup> The European Society for Intensive Care Medicine suggests prescribing 1.2-1.5 g

protein/kg/d in most adult patients on ICU except those patients with extreme losses.<sup>9</sup> Conversely, American Society for Parenteral and Enteral Nutrition (ASPEN) recommend a larger range than this for the majority of ICU patients, 1.2-2.0 g protein/kg/d. In the case of large burns, recommendations exceed 2g protein/kg/d. It is important to note that evidence was graded as level E because of a lack of high quality randomised controlled trials (RCTs).<sup>7</sup> See **Figure 1**.

## Protein and clinical outcomes

Singer<sup>10</sup> reviewed three prospective studies and the parameters used within each study. The tight calorie control study (TICACOS) looked at setting energy targets using measured energy expenditure via indirect calorimetry using both enteral and parenteral nutrition. Control patients had energy requirements based on 25 kcal/kg/body weight. Despite having targets set to achieve energy balance, the study group were slightly overfed because non-nutrient energy was not included (e.g. propofol). The results from the study showed that overfeeding resulted in an increase length of stay and ventilation, however, the trend in hospital mortality was reduced in the study group. Enteral feed and parenteral solutions have fixed energy: protein ratios, the average protein intake per day for the study group was 13 g/d higher than in the control group.<sup>10</sup>

Figure 1: The Clinical Guideline Ranges in Protein Requirements



“The main goal for protein intake is to optimise the acute phase response in terms of immunity and wound healing while protecting skeletal muscle mass and function.<sup>3</sup>”

In a *post hoc* analysis of 843 mechanically ventilated, haemodynamically stable, artificially fed ICU patients, mortality was lowest in non-septic, non-overfed patients receiving >1.2 g protein/kg/d.<sup>1</sup> One hundred and seventeen patients were diagnosed with sepsis, and when compared with the non-septic group mortality was higher (48.7% and 33.9% respectively). The non-septic patients (n =726) were categorised into an overfed group and a non-overfed group. The non-overfed group mortality was lower when protein intake was >1.2 g/kg/d when compared to the patients receiving <1.2 g/kg/d (19.1% and 34.5% respectively).

The Supplemental Parenteral Nutrition Study (SPN) by Heidegger<sup>11</sup> randomised 305 patients whom were receiving <60% measured energy expenditure to either receive supplementary parenteral nutrition or enteral nutrition alone. The intervention group had fewer infections and more antibiotic free days. There was no difference in length of stay or mortality. Again, protein intake was higher in the intervention group (79 g/d vs 56 g/d). Additionally cumulative energy balance was +124 kcal in the study group whereas the control group were in a significant energy deficit, -2317 kcals. The benefits seen in the study group may reflect those patients being fed adequate energy, protein or both.<sup>11</sup>

A recent multi-centre RCT, involving 894 critically ill patients, measured 90-day mortality in patients who were permissively underfed (40-60% of calorie requirements) or received standard enteral nutrition (70-100% of calorie requirements) where protein intake was kept similar, 57g and 59g/d of protein respectively, over 14 days.<sup>12</sup> Interestingly, there was no significant difference in 90-day mortality between the two groups. Protein requirements were based on 1.2-1.5 g/kg/body weight and despite no significant difference in 90-day mortality, patients in both the permissive underfeeding and the standard enteral feeding groups were under fed protein (68% and 69% of requirements respectively). It is difficult to apply the outcome of a large RCT when a significant protein underfeeding has occurred. The non-protein energy:nitrogen ratio (NPE: gN) of the permissive underfeeding group was lower, which may have been advantageous.<sup>13, 14</sup>

An observational study by Weijs<sup>15</sup> included 886 mechanically ventilated patients, 647 patients who were fed enterally, nine fed parenterally and the remaining 230 patients with enteral and parenteral top-up. Patients were categorised into three main groups: no

target energy or protein; energy target; or protein and energy target. The results concluded that setting and reaching personalised energy and protein requirements resulted in a 50% decrease in 28 day hospital mortality. This study highlights that optimising nutrition on ICU for calories and protein is important.<sup>15</sup>

A prospective observational study reviewing protein provision of 113 ventilated ICU patients with burns >15% Total Body Surface Area (TBSA) and severe sepsis found that those who received higher amounts of protein during admission to ICU had a lower mortality.<sup>16</sup> The researchers categorised patients into three sub groups: low, medium and high protein groups (0.79 g, 1.06 g and 1.46 g protein/kg body weight respectively). ICU mortality was lower (16%) in the high protein group when compared to the low protein group (27%). Additionally, a larger proportion of patients were discharged from ICU alive when given more protein. Neither mortality nor discharge from ICU was statistically significant.

## Safety

Based on a review of observational findings, patients with burn injuries may require up to 3 g of protein/kg/d and suffer no adverse effects.<sup>2</sup> Conversely, Jolliet *et al.*<sup>9</sup> highlight caution in prescribing >1.8 g protein/kg/d, but do not provide evidence to support this. ESPEN's recommendations for protein provision are based on Grade B evidence referenced with the parenteral nutrition recommendations.<sup>8</sup>

## Obese ICU patients

ASPEN suggest feeding higher amounts of protein to critically ill obese patients based on BMI (kg/m<sup>2</sup>) and ideal body weight – BMI 30-40: 2 g protein/kg IBW/d; BMI >40: 2.5 g protein/kg IBW/d.<sup>7</sup> This grade D evidence suggests that giving protein within this range should encourage neutral nitrogen balance and wound healing.

Despite limited evidence on calculating protein requirements on obese ICU patients, using lean body mass (LBM) may provide an alternative method for dietitians. Ideally LBM is measured using a CT scan, bioelectrical impedance or ultra sound imaging. However, these methods are not always available. Alternative methods of calculating LBM are available which can be used to base protein calculations alongside the clinically changing condition of the patient.<sup>17</sup>

The wide global variation in ICU protein recommendations is reflected in differing dietetic prescriptions. We lack definitive RCT data to guide the upper limit of protein efficacy and safety in ICU.<sup>2</sup>

## Are protein requirements met?

A prospective international study of 3390 ventilated ICU patients from 201 units in 26 countries demonstrated the challenges in providing early, adequate nutrition.<sup>18</sup> The average time to start enteral nutrition was 38.8 hours and patients only received 61.2% of calories and 57.6% of protein prescribed. The paper concluded that very few units use any volume-based feed protocols, motility agents or small bowel feeding to optimise energy and protein delivery.

Feeding on ICU is often complex due to the fluctuations of the patients' clinical condition and the frequent interruptions in feeding as a result of urgent interventions. These factors impact greatly on the ability to feed patients and one global survey reported that protein and calorie intake reach only 45-55% of the nutrition prescribed.<sup>19</sup> Feed prescriptions are focused on providing energy to meet estimated requirements while protein is a secondary target. There is also difficulty in measuring the outcomes from protein administration or interpreting biomarkers, such as nitrogen balance to measure the effectiveness of protein intake. It is suggested that the shortfall in protein intake on ICU is due in part to a failure to understand the physiological role of protein in recovery from critical illness.<sup>20</sup>

Additionally, protein requirements aren't fixed and will vary with changing clinical

condition and disease progression and so requirements need to be reviewed regularly and feeding regimens altered to reflect the changes. Locally, we base nitrogen requirements on clinical condition and level of metabolism; international guidelines offer no such guidance.<sup>21</sup>

## The practicalities of meeting protein requirements on ICU

Preliminary data suggests that enteral feeds and parenteral solutions are often unable to provide adequate protein without overfeeding energy.<sup>21</sup> It can be seen that to meet protein guidelines without exceeding energy expenditure necessitates a prescription of feeds  $\pm$  liquid or soluble protein supplements with an overall NPE:gN ratio less than or equal to the NPE:gN ratio based on the patients' energy expenditure and protein requirement (Figure 2).<sup>21</sup>

However, we lack feeds with very low NPE:gN ratios (40-80:1) necessary to meet the needs of patients that have the amount of feed prescription limited by significant non-protein energy input or requirement for hypocaloric feeding within the energy limit. In these cases protein supplementation may be mandatory to reduce the overall prescription NPE:gN ratio. In practice, complete feeds have the advantage of usually providing adequate micronutrients. Alternatively, protein supplements permit titration to meet changing protein needs,

but may require micronutrient supplementation. In both cases it should be checked that the overall prescription meets the obligatory glucose requirement to avoid possible excess gluconeogenesis.

Implementing changes to protein provision on the ICU will require education on the need and carefully thought through targets for nitrogen/protein considering route, duration and clinical implications.

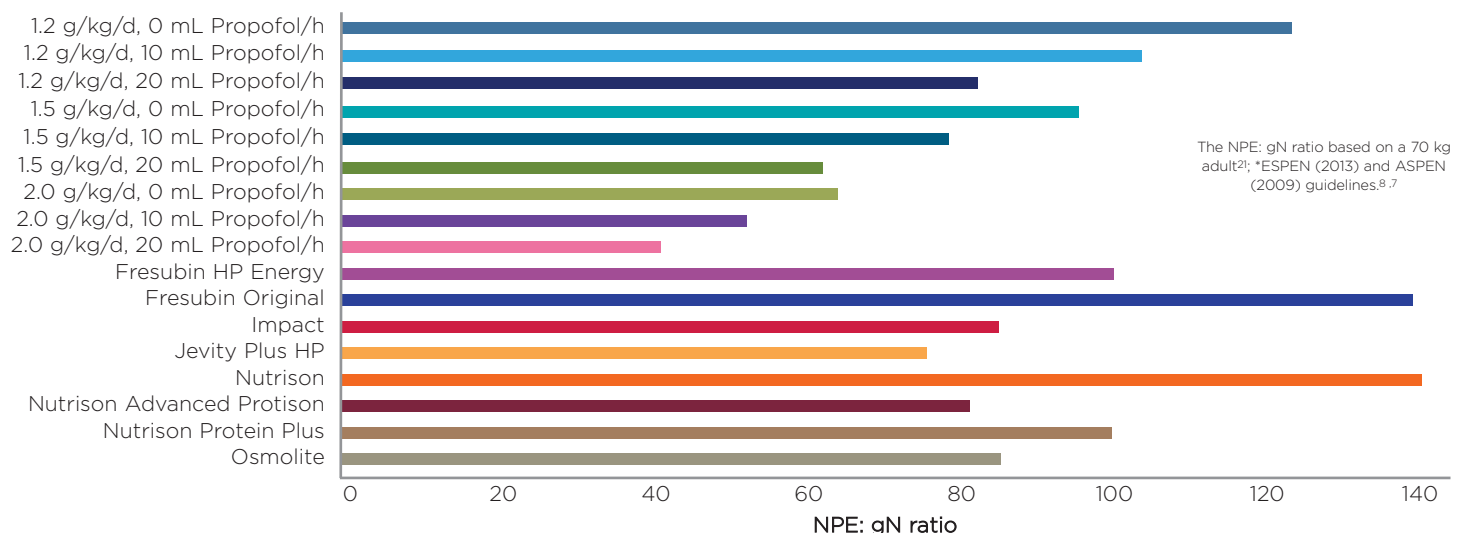
## Summary

- In critically ill ventilated patients aim for a protein intake  $>1.2$  g protein/kg/d
- Review protein requirements regularly as patient condition changes
- For obese patients consider protein requirements based on LBM or alternatively use adjusted/Ideal Body Weight in patients with BMI  $>30$  kg/m<sup>2</sup>. For BMI  $<20$  kg/m<sup>2</sup> use ideal body weight of 20 kg/m<sup>2</sup>, for BMI  $>30$  kg/m<sup>2</sup> use ideal body weight based on 27.5 kg/m<sup>2</sup>
- Consider the NPE:gN<sup>2</sup> ratio of feeds and whether to use a protein supplement to meet requirements.

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Figure 2: Non-protein Energy: Nitrogen (NPE:gN) Ratio of Protein Guidelines\* and Commercially Available Feeds



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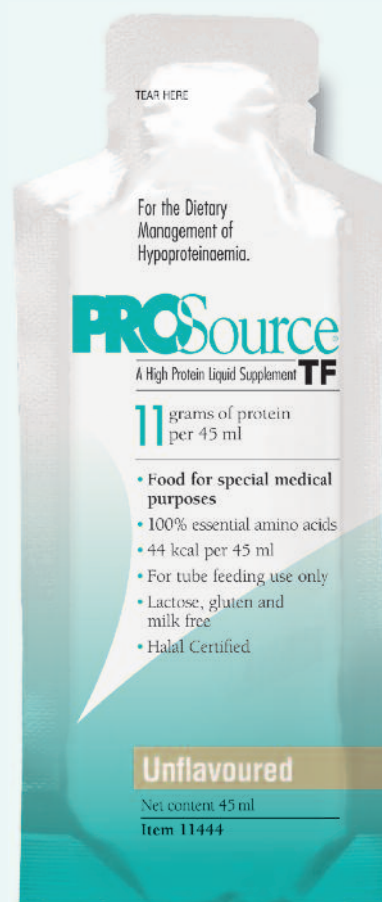
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