Enteral Protein Supplementation in Critical Illness

A review of the evidence and practical guide


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In 2016, the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM) published their joint guidelines for the provision of nutrition support to critically ill adults.[1] Given the last update of these guidelines was in 2009, and the European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines for enteral (EN)[2] and parenteral nutrition (PN) in the Intensive Care Unit (ICU)[3] are also outdated (2006 and 2009 respectively), these were heavily anticipated. At 53 pages, these are the most comprehensive critical care nutrition guidelines to date; however, of note, they only include data up to December 2013. The authors do not feel that including new data would significantly change the recommendations provided and, as should be the case with any guideline, they emphasise the need for clinical judgement and consideration of the latest evidence when faced with a patient at the bedside. Also notable is the number of recommendations based on expert opinion (54 out of 90), which is a reflection of the lack of high quality evidence available in critical care nutrition to date.

One recommendation that has raised much discussion in the critical care nutrition community is that surrounding protein targets. This review will focus on the evidence leading to these recommendations in the general ICU population and provide some practical tips on how we can meet protein targets with enteral feeding at the bedside.

What are the current recommendations?

ASPEN/SCCM[1] have recommended a protein target of 1.2-2.0 g/kg/day (actual body weight) in the general ICU population and this may be even higher in patients with poly-trauma, burns or obesity (see **Table One**).

Do current data support these high protein targets?

The ASPEN/SCCM guideline recommendations[1] are based on four studies; two prospective observational studies[4, 5] and two randomised controlled trials (RCTs)[6, 7] (**Table Two**). In summary, Weijs and colleagues[4] found a 50% reduction in 28-day mortality when both energy and protein targets were met while the same was not seen for patients who only met their energy requirements. In the second study, survival time was improved with greater provision of protein and amino acids in a dose dependent manner.[5] Again, the same effect was not seen for energy intake. These studies have contributed to the hypothesis that it is high protein intakes driving the beneficial effects of nutrition support in the critically ill over the first week of admission.

The two, small, RCTs focused on the effects of protein intake on nitrogen balance.[6, 7] Whilst both studies found that higher protein intakes led to more positive nitrogen balance, one study is from 1985,[7] and both were performed in special populations (head injury and continuous renal replacement therapy), thereby reducing the generalisability to the wider ICU population. Although commonly used as a surrogate measure for protein utilisation, nitrogen balance is of limited use in the critically ill population due to the inability to account for skin and faecal losses in the final calculation.[8] In addition, this method is not reflective of gains or losses in muscle mass, which is an important consideration when determining a benefit from protein intakes in this population.

Table One: International Guideline Recommendations for Protein Targets in the Critically Ill

ASPEN/SCCM Guidelines[1]	
General ICU	1.2-2.0 g/kg/day
Obesity	
BMI 30-40 kg/m^2	2.0 g/kg/day (IBW)
BMI ≥40 kg/m^2	2.5 g/kg/day (IBW)
CRRT	Up to 2.5 g/kg/day
Traumatic brain injury	1.5-2.5 g/kg/day
Burns	1.5-2 g/kg/day
ESPEN Guidelines[3, 37]	
General ICU	1.3-1.5 g/kg/day (IBW)
CRRT	1.5-1.7 g/kg/day
Canadian Critical Care Practice Guideline (2015)[9]	
Insufficient data to make a recommendation	

BMI=Body mass index; ICU = Intensive care unit; CRRT = Continuous renal replacement therapy

The low quality of this evidence, and the lack of a recommendation provided in the Canadian Clinical Practice Guidelines for Nutrition Support in the Critically Ill,[9] have led to much debate surrounding this topic.

Have any relevant studies been published since 2013?

Several studies have been published since 2013 investigating optimal protein intakes in critical illness (**Table Three**). Whilst there is one RCT,[10] the majority have been observational.[11-14] Similar to the studies informing the 2016 ASPEN/SCCM guidelines, there appears to be a consistent association between higher protein intakes and a reduction in mortality. However, the most appropriate time to meet these targets remains unknown. In addition, benefits may only be seen in patients who are considered high nutritional risk.[15]

Is it all about mortality?

While useful, current studies investigating optimal protein intakes focus predominantly on mortality as an outcome. However, as we see survival from critical illness increasing,[16] we are also seeing increasing numbers of patients being discharged from hospital with physical and functional disability and poor quality of life.[17, 18] Although the relationship is poorly understood, the profound muscle wasting that occurs during critical illness may be partly responsible for these disabilities and it is here that nutrition, in particular protein intakes, may prove beneficial.

To date, only one prospective RCT has investigated the impact of different protein intakes on patient-centred outcomes in critically ill patients.[19] Whilst higher protein intakes led to significant improvements in handgrip strength, muscle wasting and fatigue score in patients receiving higher protein intakes (0.9 g/kg/day *vs.* 1.1 g/kg/day), this study was limited to patients receiving parenteral nutrition only and, therefore, is not generalisable to those receiving enteral nutrition alone. Despite this and some additional methodological limitations, namely the target amino acid intakes not being reached in either group, this study should encourage researchers to utilise similar outcomes in future trials.

Could high protein intakes actually be harmful in critical illness?

The results of the aforementioned studies are in contrast to other observational and *post hoc* analyses indicating that protein may not influence muscle wasting and recovery in critical illness. In two pre-planned sub-studies of the large EPaNIC Trial[20] delayed supplemental PN (SPN) did not affect rates of muscle wasting[21] and was found to be associated with reduced weakness compared to those who received early SPN (i.e. less protein led to better outcome).[22] The biological process driving these outcomes is thought to be incomplete activation of autophagy caused by administration of amino acids early in critical illness.[23] However, this is yet to be studied prospectively and it is unclear whether provision of enteral protein elicits the same response.

Lastly, in the MUSCLE UK study, investigating acute skeletal muscle wasting in early critical illness, higher protein intakes were found to be associated with higher rates of muscle wasting.[24] Given the observational nature of this study, these data can only be hypothesis generating. Indeed, these data have led to the hypothesis that it is not the amount of protein that is important, but the provision of continuous feeding that has led to this effect and intermittent feeding may in fact reduce muscle wasting.[25] The basis for this is a concept called the 'muscle full effect', which is apparent in healthy individuals, whereby on ingestion of an oral whey protein bolus or administration of parenteral amino acids, muscle protein synthesis triples between 45-90 minutes before returning to baseline.[26, 27] This return to baseline occurs even in the presence of the continued availability of amino acids in both the plasma and muscle. These data may indicate that simply providing continuous amino acids in critical illness may not physiologically be able to influence muscle wasting. The reader is directed to **www.clinicaltrials.gov** (NCT02358512) for more information regarding a current study investigating this in the United Kingdom.

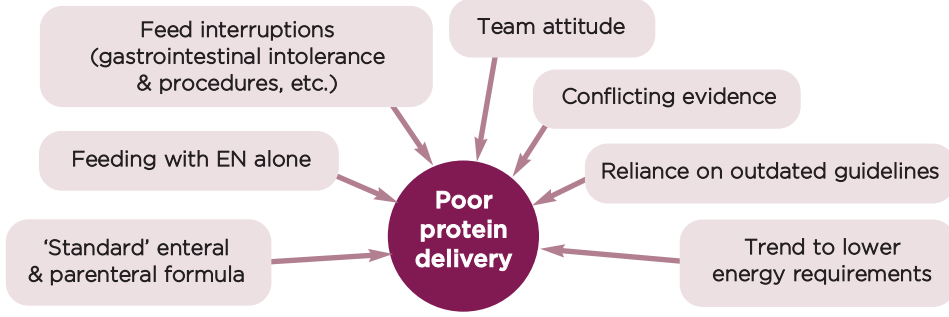
What should we do in practice?

Considering current guideline recommendations and studies published after 2013, it would seem reasonable to aim for the higher protein targets by at least day 4 of ICU admission until further evidence is available. In this regard, it may be suitable to allow patients to simply be fed using the feeding protocol up until 48-72 hours of admission before an individualised feeding regimen is devised, considering factors which may influence nutrition risk[15, 28, 29] and appropriate methods to meet these targets.

Several barriers exist in clinical practice which preclude these high protein targets being met easily (**Figure 1**). Most commonly, it is the lack of appropriate enteral feeds containing appropriate non-protein energy to nitrogen ratio (NPE:gN). Typically, 'standard' (1 kcal/mL) enteral feeds are not suitable and enteral feeds containing high protein (NPE:gN of 80:1 - 100:1) will need to be utilised. However, when also taking into consideration non-nutritional energy (propofol, citrate, intravenous glucose), kilocalories from EN may need to be restricted resulting in a significant protein deficit and the need for using protein supplements.

There are several protein supplements available on the market, in both powder and liquid forms. A liquid supplement is ideal for enteral tube feeding because of ease of administration, since powdered protein can be difficult to dissolve in water. Of course, it is also important to consider the protein source and it's acceptability to the patient and their preferences (e.g. bovine/porcine, Kosher, Halal, dairy-free). There is no current recommendation on the quality of protein that should be provided to critically ill patients. Although some amino acids are in greater demand in critical illness,[30] there is not enough evidence to support supplementation of individual amino acids. A protein supplement that contains all of the essential amino acids is assumed to be optimal. Specifically, the protein supplement should have a high leucine content. Leucine is an anabolically potent amino and it is thought that the ratio of leucine in relation to isoleucine and valine should be at least double.[31] A study by Borsheim *et al.*[32] found that a protein supplement with five times the amount of leucine, compared to isoleucine and valine, prompted increased muscle protein synthesis in glucose-intolerant elderly individuals, although this is yet to be confirmed in critical illness.

Figure 1: Challenges of Meeting High Protein Intakes in Critical Illness



The main protein supplements available on the market are either based on whey or collagen proteins. Whey has a high concentration of branched chain amino acids (BCAAs) and is therefore considered a complete protein.[33] In contrast, collagen has a low concentration of BCAAs and is regarded as being of low biological value with an inference that whey would perform superiorly to collagen in terms of muscle protein synthesis.[34] However, in a comparison of whey *versus* fortified collagen hydrolysate protein supplements, nitrogen balance was better maintained in older adults who received the collagen supplement.[35] This trial was small in numbers and there is limited other data comparing both substrates. Nonetheless, a recent paper published last year showed that using a liquid protein supplement, in addition to a high or very high protein EN, helped to increase the number of patients who met their protein prescription and is a useful strategy in clinical practice.[36]

Conclusion

Current evidence suggests that achieving protein targets by day 4 of ICU admission may be beneficial in patients who are expected to remain on the ICU for up to a week or longer. However, significant barriers exist when it comes to meeting these targets. Individualised nutrition assessment should include appropriate strategies to overcome these barriers, including the use of appropriate enteral feeds and protein supplements. Both energy and protein targets and balances should be re-assessed throughout a patient's stay with enteral feed and supplementation adjusted accordingly to avoid potential complications. Further, prospective RCTs are urgently required to ascertain the effect of high protein intakes on muscle wasting and long-term outcomes of ICU patients.

Table Two: Details of Studies included in the ASPEN/SCCM Guideline Recommendations for Protein Intakes in the Critically Ill

Author	Study Design	Population	Nutrition Targets	Primary Outcome
Clifton *et al.*, 1985[7]	RCT	N=20 Head injury	Energy: 140% or measured energy expenditure (~3500 kcal/day) Protein: 14% or 22% of energy from protein	Nitrogen balance
Scheinkestel *et al.*, 2003[6]	RCT	N=50 CRRT	Energy: Schofield + stress factors or indirect calorimetry Protein: 1.5 g/kg, 2.0 g/kg or 2.5 g/kg	Nitrogen balance
Weijs *et al.*, 2012[4]	Prospective observational	N=886 Medical and surgical ICU	Energy: Indirect calorimetry Protein: 1.2 g/kg	28-day mortality
Allingstrup *et al.*, 2012[5]	Prospective observational	N=113 General ICU	Energy: 25-30 kcal/kg or indirect calorimetry Protein: 1.2-1.5 g/kg or guided by 24 hour urinary urea excretion	10-day in-ICU mortality

RCT = Randomised controlled trial; ICU = Intensive care unit; CRRT = Continuous renal replacement therapy

Table Three: Details of Studies Published after 2013 Investigating Optimal Protein Intakes in Critical Illness

Author	Study Design	Population	Nutrition Targets	Primary Outcome
Rugeles *et al.*, 2013[10]	RCT	n=80 Mechanically ventilated ICU	Group 1: 15 kcal/kg and 1.7 g/kg protein Group 2: 25 kcal/kg and 20% kcal from protein	Change in SOFA score
Weijs *et al.*, 2014[11]	Prospective observational	n=843 Non-septic ICU	Energy: Harris-Benedict (10% AF, 20% SF) or indirect calorimetry; Protein: 1.2-1.5 g/kg (adjusted for obesity)	Hospital mortality
Elke *et al.*, 2014[12]	Prospective observational	n=2270 Mechanically ventilated with sepsis and/or pneumonia	Institution targets	60-day mortality
Nicolo *et al.*, 2015[13]	Prospective observational	n=4040 Mechanically ventilated and LOS <4 or 12 days	Institution targets	60-day mortality
Ferrie *et al.*, 2016[19]	RCT	N=119 ICU patients requiring PN	Energy: ~25 kcal/kg Protein: 0.8 g/kg *vs.* 1.2g/kg	Handgrip strength at ICU discharge
Song *et al.*, 2017[14]	Prospective observational	n=211 Mechanically ventilated ICU	Energy: 25 kcal/kg (adjusted for obesity) Protein: 1.2-1.5 g/kg	ICU mortality

RCT = Randomised Controlled Trial; LOS = Length of Stay; ICU = Intensive Care Unit; AF = Activity Factor; SF = Stress Factor; SOFA = Sequential Organ Failure Assessment Score; PN = parenteral nutrition

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