Developments in Protein Provision in Critical Care


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There are few areas of absolute consensus when it comes to nutrition in the critically ill, due to the challenges of conducting high quality randomised controlled trials (RCTs) and finding strong signals in such a heterogenous patient population. Protein is no exception.[1,2] Protein catabolism is increased as a consequence of critical illness, which leads to rapid and severe skeletal muscle wasting.[3] This skeletal muscle wasting is, in turn, associated with intensive care unit (ICU)-acquired weakness.[4,5] For this reason, there is widespread acceptance that protein targets should be higher in the critically ill than in the general population in order to attenuate skeletal muscle wasting. However, there is still some way to go before consensus is reached on what those ideal targets should be, particularly in specific critical care subsets such as those following trauma or receiving continuous renal replacement therapy.

The last time critical care protein targets were discussed in detail in CN was in 2017, following the publication of the 2016 ASPEN guideline.[6] Since then, ESPEN guidance has been updated and several relevant systematic reviews published to help inform our practice in specific patient categories.[1,2,7,8] In this review we will provide a summary of recent guidelines, studies, and the key recommendations for future research design for protein dosing trials in the critically ill.

Current guideline recommendations

The most recently updated of the major critical care nutrition guidelines is ESPEN, which recommends the following regarding protein provision in critical care:[7]

During critical illness, 1.3 g/kg protein equivalents per day can be added progressively.

This recommendation is based largely on observational data using mortality as the primary outcome (the limitations of which will be discussed later in this article) and is slightly higher than the minimum level recommended in the ASPEN guidelines.[6] This increased recommendation is following the publication of a large, retrospective observational study of nearly 1,200 critically ill adults which showed significant improvements in 60-day mortality with protein administration of more than 1.3 g/kg/day.[9] Recommended protein intakes by clinical condition as recommended by the different guidelines have been summarised in **Table 1**.

Table 1: Current recommended protein intakes in critical care guidelines

Critically ill population		Recommended protein intakes
General ICU		1.2-2.0 g/kg/day[6] 1.3 g/kg/day[7]
Burns		1.5-2.0 g/kg/day[6,7]
Obesity		1.3 g/kg adjusted BW/day[7] BMI 30-40: 2.0 g/kg ideal BW/day BMI >40: 2.5 g/kg ideal BW/day[7]
Renal*	Hospitalised patient with AKI, AKI on CKD, CKD, with acute/critical illness not on KRT	Start with 1 g/kg/day and gradually increase to 1.3 g/kg/day if tolerated[10]
	Critically ill patients with AKI or AKI on CKD or CKD with KF on conventional intermittent KRF	1.3-1.5 g/kg/day[10]
	Critically ill patients with AKI or AKI on CKD or CKD with KF on CKRT or PIKRT	1.5-1.7 g/kg/day[10]
Trauma		Higher end of 1.2-2.0 g/kg/day[6] 1.5-2.0 g/kg/day[7] No reported benefits >2.2 g/kg/day
Traumatic Brain Injury		1.5-2.5 g/kg/day[6]

Key: • AKI – acute kidney injury • BW – body weight • CKD – chronic kidney disease • CKRT – continuous kidney replacement therapy • ICU – intensive care unit • KF – kidney failure • KRF – kidney replacement therapy • PIKRT – prolonged intermittent kidney replacement therapy

*For renal patients, the recommendation is to use pre-hospitalisation BW or usual BW instead of ideal BW. Actual BW should not be used for a protein prescription[10]

Outcome choice for trials investigating protein provision in the critically ill

Mortality has traditionally been used as the primary outcome in ICU research, including nutrition trials, and is often required by regulatory authorities.[11] However, it is now acknowledged that mortality may not be the most appropriate outcome for nutrition interventions, especially with improving ICU survival rates and the focus on longer term, functional outcomes.[12] Furthermore, the biological plausibility that a single nutrition intervention will have a significant effect on mortality is low, especially in the context of a median length of stay for critically ill patients of less than one week and mortality rates that are fairly low.[13, 14]

Muscle is the largest protein pool in the body, and muscle protein catabolism is known to increase in critical illness.[7] On ICU, this proteolytic activity can significantly outweigh protein synthesis, leading to rapid and severe wasting of skeletal muscle.[3, 4] When accompanied by impaired muscular repair, this in turn is associated with sustained, ICU-acquired weakness.[4, 5] This is one of the key components of Post Intensive Care Syndrome (PICS), which encompasses the profound physical, cognitive and psychosocial impairments that may present for months, or even years, after ICU admission.

It is therefore biologically plausible that higher protein intakes may improve muscle protein synthesis, thereby reducing the net catabolic impact, attenuating muscle wasting, and improving functional outcomes and subsequently, quality of life, after critical care.[11, 14, 15]

Muscle wasting and functional outcomes are therefore increasingly of interest in studies investigating protein doses in the critically ill. However, the use of such measures as primary outcomes can be challenging, not least due to the difficulties of obtaining and measuring baseline measurements in these parameters, and the absence of validated tools for evaluating post-ICU physical function.[14]

Table 2 (*see page 28*) summarises a range of potential outcome measures for nutrition trials that relate to muscle wasting, strength, and functional status, and the advantages and disadvantages of each.[14]

Protein dose and mortality outcome

A number of observational studies have suggested an inverse relationship between protein delivery and mortality, where mortality has been the primary outcome.[16-19] Evidence from observational studies is always stronger when supported by RCT findings. As yet, clear associations between protein dose and mortality have not been seen in published RCT, but studies to date were either not specifically designed to compare two different protein doses, or didn't use mortality as a primary outcome.[20-22] As such, we are still awaiting published RCT that are specifically designed to look at this relationship.

Adding to this, three recent systematic reviews found no significant effect of protein dose on mortality risk.[1, 2, 8] However, limitations exist in terms of heterogeneity, study design, and importantly, protein dose. In Fetterplace *et al.* (2020),[2] for example, the protein 'intervention' group was a mean of 1.3 g (SD 0.08) protein/kg/day, with 'usual care' a mean of 0.75 g/kg/day (SD 0.15), whereas in Davies *et al.* (2017),[1] the mean 'high' and 'low' protein groups were 1.02 g/kg (SD 0.42) and 0.67 g/kg/day (SD 0.38), respectively. While these numbers may reflect the practical realities of prescription versus delivery in terms of enteral nutrition on ICU, they are, at best, near the bottom end of the protein targets recommended in current guidelines, and perhaps therefore also contribute to the lack of observed effect.

To further illustrate the impact of subject heterogeneity, a recent retrospective observational study demonstrated that early administration of high protein (mean protein intake >1.2 g/kg/day on ICU admission days 2-4) was associated with lower mortality in critically patients than low protein (mean protein intake <1.2 g/kg/day on days 2-4) – but only for those patients with low skeletal muscle mass and density, measured using routinely available CT scans at admission.[23] This association was significant for both 60 day (p=0.001) and six-month mortality (p= 0.02) but was not seen in those with either normal skeletal muscle density or area.[23] This study sets the hypothesis that there may be a group of patients who will benefit more from higher protein intakes and this requires exploration in an RCT setting.

Protein dose and muscle related and functional outcomes

Good quality RCT investigating protein dose and muscle related outcomes are sparse, meaning that neither firm recommendations in major guidelines, nor meta-analysis in systematic reviews exploring this association have been possible.[2,6-8]

That said, some promising results have been seen in individual studies. Fetterplace *et al.* (2018),[24] found a significant reduction in loss of quadriceps muscle layer thickness at discharge in a higher protein group (mean 1.2 (SD 0.30) g/kg/day) compared to low protein (mean 0.75 (SD 0.11) g/kg/day), as measured by ultrasound. However, the same study found no significant effect of protein dose on hand grip strength, muscle strength, ICU acquired weakness or physical function on ICU, although there was missing data in up to 80% of participants. Moreover, these were all secondary outcomes, and should therefore be considered hypothesis-generating results only.

Similarly, a 2016 RCT of parenteral protein delivery demonstrated that higher protein delivery (mean 1.17 (SD 0.21) g/kg/day) vs. lower protein delivery (mean 0.87 (SD 1.17) g/kg/day) resulted in greater muscle thickness measured by ultrasound on day seven following randomisation.[22] This effect was seen when looking at the sum of three muscle sites (forearm, biceps and thigh, p=0.02) and forearm muscle thickness (p=0.0001). There was also significantly improved handgrip strength at day seven in the higher protein group (p= 0.025), but this effect was no longer significant on discharge from ICU (p=0.054). Again though, when interpreting these results, it is important to note that these were all secondary outcomes.

Current research

A review of the current trials, registered on a single clinical trials database (https://clinicaltrials.gov/), investigating the role of protein dosing on outcomes from critical illness, has identified these current themes:

- Reducing the severity of ICU acquired weakness by early intervention with high protein enteral nutrition together with mobility.
- The effect of high versus standard protein provision on functional recovery of critically ill patient by focussing on functional, patient centred outcomes.

- If protein supplementation improves markers of anabolism and protein synthesis.
- The effect of supplemental protein to achieve higher intakes (> 2.0 g/kg/day) and all-cause mortality at varying days (60-90).
- The influence of bolus nutrition on skeletal muscle metabolism.
- Impact of low calorie, low protein feeding during the acute phase of shock.
- The combined approach of combined cycle ergometry and IV bolus amino acid supplementation on muscle mass.

Of the RCTs focusing on protein dose currently recruiting, it is evident that there is still wide variability in primary outcome measures being used. For example, of the five studies investigating high (>2.0 g/kg/day) versus low (<1.3 g/kg/day) protein doses in critically ill patients, two are using mortality as the primary outcome (NCT04475666, NCT03160547), with one using ICU length of stay (NCT03573739). Another is using serum concentrations of transthyretin as a circulating biomarker of nutritional status and protein synthesis (NCT03170401), despite recent evidence suggesting that this has limited value.[12] Of the five RCTs, only one has a health-related quality of life primary outcome measure (NCT04633421).

Synergistic therapy studies that use a combination of nutrition and physical activity intervention with a functional primary outcome are seen as the future of critical care nutrition research.[25] There are four studies currently open to recruitment using this dual approach. Two are using an enteral route (NCT04261543, NCT03469882) and two are using boluses of IV amino acids (NCT04099108, NCT03021902). Interestingly, all four are using functional- or muscle-related primary outcomes, but all are different. Outcomes include change in muscle size and depth via ultrasound (NCT04261543, NCT04099108), physical component summary three and six months after randomisation (NCT03469882) and six-minute walk distance at hospital discharge (NCT03021902).

To overcome the challenges in determining appropriate and patient centred outcomes for nutrition research in critical care, a core outcome set (COS) has been proposed in line with other areas of critical care research.[14]

'A core outcome set is an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or healthcare'.[26]

As discussed in this review, there is a wide and varied spectrum of objectives and outcomes of RCT assessing nutritional interventions in critically ill patients and the use of COS may help to compare nutritional strategies, effectively pool data from different studies on the same condition, and encourage more complete reporting of outcomes. This will also allow for comparison between studies and to conduct meta-analyses.[11, 14] Work is already in progress with international nutrition experts, to develop critical care nutrition COS.[27] This study will expand on outcomes initially identified in a systematic review, and include further research from August 2018 to present day.[14]

Conclusion

Where does all that leave us? More questions than answers, maybe, but absence of robust RCT evidence is certainly not evidence of absence, and we are hopeful that large international trials will help to shed light on optimal protein dosing in different stages of a critical care admission.

In the meantime, the recommendations in major guidelines of 1.2-2.0 g/kg/day remain appropriate for use in the general ICU patient, with the most recently updated of these, ESPEN, stipulating 1.3 g/kg/day as the recommended target.[6, 7]

With current protein recommendations across all clinical groups based almost exclusively on observational data, we must hope and aim for high quality RCTs with a good level of homogeneity in terms of study design, where protein is investigated in isolation rather than alongside energy dose, and crucially, with longer term, relevant, muscle-related and functional outcomes routinely measured. This is essential, as ICU survival rates continue to improve.

Finally, but crucially, we need to acknowledge that setting protein targets are one thing, but achieving them is another, and many of these studies demonstrate this all too clearly, with protein delivery often falling well below the levels recommended in major guidelines. This limits the conclusions that can be drawn from them. As we know, prescription does not equal delivery, but that is a topic for another article.

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Table 2: Outcome measures relating to muscle wasting, strength or physical function that have been proposed for use in nutrition trials in critical care

Outcome measure	Method	Advantages and disadvantages
Muscle strength	Handgrip dynamometry	• Needs strength and participator effort to hold dynamometer stable, but requires minimal patient re-positioning. • Controversy if hand grip strength is representative of overall strength. • Variation in method used makes comparison between studies difficult. Requires standardised approach. • Can be used to identify ICU acquired weakness.
	Medical Research Council sum score	• Assesses strength, but patients may learn to be functional in the absence of strength. • With training, physicians can generate highly reproducible results. • Results influenced by cognitive dysfunction such as delirium. • Requires patients to be fully awake to able to participate and follow commands.
Muscle mass or lean mass	Computed tomography (CT)	• Analysis of skeletal muscle in a single CT could be carried out if patient has already undergone abdominal CT scan, however routine use is difficult due to cost, time, radiation exposure and risk of transporting acute patients. • Reduced feasibility for follow up measurements in acute care patients. • Cut off points for low skeletal muscle area associated with mortality have been defined in ICU patients.
	Magnetic resonance imaging (MRI)	• Technique is free of ionising radiation and could allow patient to have repeated scans. • Cannot be used if patient has equipment that cannot enter a magnetic field. • Not useful if patient cannot hold breath. • Limited to use in highly specialised settings. • Costly and requires specific
	Musculoskeletal ultrasound	• Relatively inexpensive, but can be difficult to acquire high quality images. • Can (only) monitor specific muscle groups, instead of whole body lean mass. • Good inter/ intra observer reliability has been reported. • Muscle quality has been correlated with muscle strength. • Lack of standardised protocols. • Influenced by oedema. • Needs to be established whether a change in muscle size/depth/area can be translated into a relevant clinical outcome.
	Deuterated creatine	• Measures total body creatine pool size. • Can be assessed in large number of subjects with very little subject burden. • Useful when CT or MRI cannot be used. • Less influenced by obesity and aging.
	Spot urine test	• Additional research required before test can be used clinically.
	Urinary 3 methylhistidine, plasma phenylalanine	• Limited introduction into clinical practice. • Presence of 3 methylhistidine in the urine does not necessarily reflect the specific breakdown of myofibrillar protein as it also released from tissues other than skeletal muscle. • Evidence suggests plasma phenylalanine correlates well with nitrogen balance in burns patients, but at present there is insufficient data to recommend its use as a reliable marker of protein turnover. Obtained via arterial puncture which is an invasive procedure.
Physical function	Six-minute walk test	• Easy to perform, reproducible, inexpensive. • Can be difficult to recruit sufficient patients that are able to complete the test due to impairment. • Can be time consuming as test requires 30 minute break between two required tests.
	Chelsea critical care physical assessment tool (CPAx)	• Score shows strong associations with hospital- discharge destination. • Short time required for assessment, minimal use of equipment.
	Functional status score for the intensive care unity (FFS-ICU)	• Has been shown to have strong inter-observer reliability. • Ability to use in long term follow up may be impacted by ceiling effect.
Functional self sufficiency	Barthel activities of daily living index	• Risk of detection bias. • Quick to administer, good reliability and validity in stroke patients but testing is inconclusive in ICU patients. • Can lack sensitivity to clinically meaningful change in ICU patients.
	Functional independence measure	• Assesses physical and cognitive disability. • Derived from extensive research with large sample sizes. • Requires training to ensure reliability.
	Quality of life scales	• Could be influenced by events occurring throughout the patient's life. • Not yet clear how changes in these measures should be interpreted over long periods.