Protein supplementation in critical illness: why, when and how?

Protein supplementation in critical illness: why, when and how?

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Purpose of review
In critically ill patients, optimal protein provision remains a challenge given the wide range in recommended protein delivery in international guidelines and the lack of robust, high quality evidence. As patients are confronted with poor functional outcomes after admission, often attributed to muscle wasting and persisting for multiple years, there is a pressing need for optimal nutritional strategies in the ICU, particularly including protein. This review will discuss the recent literature with regard to purpose, timing and mode of protein delivery.

Recent findings
Recent studies on the effect of dose and timing of protein on clinical and functional outcomes are largely observational in nature and the protein delivery considered as ''high'' still often only nears the lower end of current recommendations. The majority of trials observed no effect of protein supplementation on mortality, muscle strength or function, though some report attenuation of muscle volume loss, especially when combined with muscle activation. There is no strong evidence that ICU patients should receive supplementation with any specific amino acids.

Summary
Though adequate protein provision is likely important, it is difficult to come to a uniform conclusion regarding dosing and timing due to conflicting results in mostly observational studies as well as different cut-off values for high, moderate and low protein intake. This topic is currently subject to large clinical trials.

Keywords
amino acids, critical illness, functional outcomes, nutritional strategies, protein supplementation

INTRODUCTION

The optimal protein provision to critically ill patients remains unclear and protein requirements most likely differ for patients with varying diagnoses and in different phases of their disease course. Recent international critical care nutrition guidelines recommend that critically ill patients receive protein at a dose of 1.2–2.0 g/kg of body weight/day [1▪,2]. However, the evidence for this recommendation is weak with a paucity of high quality randomized controlled trials (RCTs) to support it. There is an urgent need for strong evidence regarding the optimal dose and type of protein supplementation and possible changes in protein requirements during the course of critical illness.

The aim of this review is to describe the importance of protein supplementation in critical illness, the recent developments in the understanding of protein absorption and metabolism and to provide insight into timing and mode of protein delivery (as a macronutrient or amino acids), with the purpose of providing practical guidance for clinicians at the bedside, essentially answering the questions: ''why, when and how?'' (Fig. 1).

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KEY POINTS

- Critically ill patients demonstrate anabolic resistance to dietary protein in absence of malabsorption, highlighting an important therapeutic target in the prevention of muscle wasting.
- Benefits of early high protein provision remain controversial due to a lack of robust data.
- There is limited evidence to support the use of specific amino acids to improve outcomes in the ICU.
- Several large randomized clinical trials are being performed to establish the effect of high protein delivery on clinical and functional patient centred outcomes.
- Protein supplementation in combination with muscle activation, such as electrical muscle stimulation or physical therapy, should be further explored.

WHY SHOULD WE SUPPLEMENT PROTEIN?

Survivors of the intensive care unit (ICU) often experience poor functional outcomes that can persist for many years after discharge and result in impaired quality of life, increased healthcare use and delayed return to work [4,5,31]. Optimal maintenance of nutritional status during ICU admission is seen as one of the key elements to improve these functional outcomes, as functional deficits are often attributed to severe muscle wasting [5]. Despite their importance, actual nutritional targets are frequently not met due to feed interruptions, gastrointestinal intolerance or feeding protocol deviations with the typical amount of protein actually delivered approximating 0.6–1.2 g/kg/day [6▪▪,7,8]. In light of this, the provision of 1.2 g/kg/day of protein is in most retrospective observational studies regarded as ''high protein'' nutrition.

The evidence for the benefit of increased protein supplementation is hitherto still limited to observational data and some small RCTs that have not been adequately powered to detect relevant differences in clinical outcomes. Zusman *et al.* [9] demonstrated a linear association between protein intake and long-term survival, suggesting that the optimum protein dose for critically ill patients is even higher than the pragmatically determined amount of 1.2 or 1.3 g/kg/day [1▪,2]. Multiple retrospective studies, both in the past and more recently, have shown a beneficial effect of protein on mortality [8,10], muscle mass and strength [11] or patient-centred outcomes[12], yet another cohort ($n = 32$) did not show an association between protein delivery and degree of muscle loss [13].

A large meta-analysis of 19 RCTs ($n = 1731$ participants) by Lee *et al.* [14▪▪] found no difference in mortality or other clinical or patient-centred outcomes between higher and lower protein doses (pooled mean protein 1.3 ± 0.48 vs. 0.9 ± 0.30 g/kg/day, respectively) with similar energy delivery. The majority of included studies were at moderate risk of bias, with small sample sizes and single centre design. Of note, the protein delivery in the 'high protein' group still only nears the lower end of current recommendations. They did find, in five small studies ($n = 273$), significantly attenuated muscle loss (mean difference −3.44% per week, 95% confidence interval [CI] −4.99 to −1.90) when patients were provided with higher protein intake. A recent review [15] has summarized all RCTs investigating dietary protein interventions on muscle mass, strength or function. The four most recent of these six RCTs failed to demonstrate any beneficial effect of protein supplementation

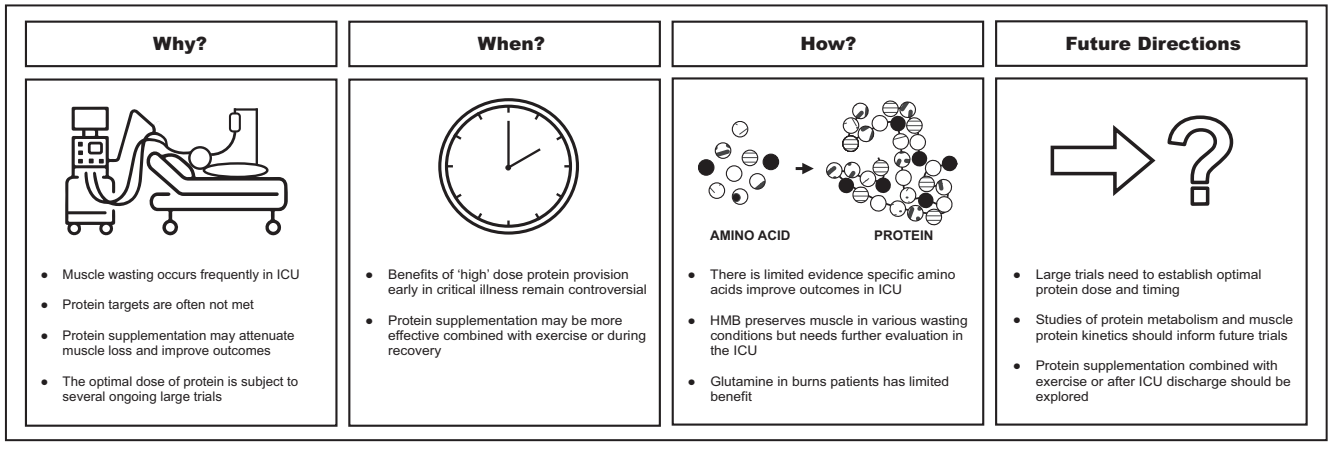

FIGURE 1. A summary of the recent evidence for the rationale, optimal timing and methods of protein supplementation in critical illness. ICU, intensive care unit; HMB, β-hydroxy-β-methylbutyrate.

[16▪▪,17,18▪,19▪]. Other recent meta-analyses also have not reported improved outcomes with higher protein delivery [20▪,21], but these included studies with significant differences in calories between groups or studies that tested immunonutrition, both of which may have confounding effects on patient outcomes.

More recently, the first RCT using computed tomography to evaluate diaphragm atrophy in 41 patients with high (1.7 g/kg/day) vs. standard (1.1 g/kg/day) protein provision, found a significant difference in recovery of diaphragm muscle mass at weeks 4 and 5 of ICU, after a similar degree of atrophy occurred during the first three weeks [22▪]. These findings would suggest additional protein supplementation does not protect from diaphragm atrophy, yet aids in its recovery. However, this did not translate in improvement of other endpoints such as weaning from mechanical ventilation, ICU length of stay or mortality. Of note, this was an open-label study and calorie delivery differed significantly between the standard and high protein intake groups (26 vs. 33 kcal/kg/day, $P < 0.001$), indicating possible bias and confounding. Lastly, only 7 vs. 7 and 3 vs. 4 patients contributed data on diaphragm muscle mass in weeks 4 and 5, and this loss to follow up potentially compromises the validity of the study findings.

Currently, several large RCTs addressing the effectiveness of high dose protein supplementation on clinical and functional patient-centred outcomes are being performed and will provide robust data to inform future clinical practice guidelines: PRECISe-trial (2.0 vs. 1.2 g/kg/day of protein via isocaloric enteral nutrition (EN); NCT04633421; recruiting), TARGET-PROTEIN [23▪] (isocaloric enteral feeds with protein content 100 g/l vs. 63 g/l; ACTRN12618001829202; recruiting), EFFORT and EFFORT-outcomes [24] ($\geq$2.2 vs. $\leq$1.2 g/kg/day of protein via EN, parenteral nutrition (PN) or both; NCT03160547 and NCT04931940).

PROTEIN ABSORPTION AND METABOLISM

Research on nutrition in critical illness has generally focused on the actual amount of nutrients administered to patients. However, studies utilizing glucose and lipid tracers suggest that maldigestion and malabsorption are frequently encountered in critical illness, which may severely jeopardize nutritional adequacy despite the administration of a targeted amount of nutrition [25].

Van Gassel *et al.* [26▪▪] studied protein absorption in critically ill patients and healthy volunteers that received an enteral bolus of 4 g of protein and a 3-*O*-methyl-D-glucose (3-OMG) tracer. They found a blunted rise in plasma levels of essential amino acids in ICU patients after the administration of the study feed. However, after one hour, essential amino acid levels were identical in both groups. Interestingly, 3-OMG plasma levels rose less sharply and remained lower in critically ill patients than in healthy volunteers for at least 150 min, suggesting glucose malabsorption is not invariably accompanied by protein malabsorption. Chapple *et al.* [27▪▪] compared protein digestion, absorption and postprandial muscle synthesis in 15 critically ill patients vs. 10 healthy controls, by providing stable isotope tracers of the essential amino acids phenylalanine and leucine intravenously, followed by a bolus of labelled intact protein intraduodenally. In line with the findings of van Gassel *et al.*, a higher and more rapid peak of exogenous phenylalanine appearance was found in healthy controls that equalised between both groups during the 6 h postprandial period. These findings suggest that protein absorption is not severely impaired in the critically ill. They did, however, find that the incorporation of dietary protein into myofibrillar protein in muscle biopsies was 60% less in critically ill patients, demonstrating anabolic resistance to dietary protein. Of note, muscle breakdown rates were not studied here and might provide an alternative therapeutic target, as pointed out by Puthucheary *et al.* [28] in their commentary.

Whether anabolic resistance can be overcome by increasing protein provision remains to be evaluated. It may be that impaired synthesis or increased breakdown are not affected by protein supply, in which case muscle catabolism should rather be treated with interventions directed at overcoming anabolic resistance than with enhanced protein nutrition.

TIMING OF PROTEIN SUPPLEMENTATION

When to start or increase protein supplementation is controversial, since several studies have cast doubt on the safety of high protein provision in critical illness. A posthoc analysis of the EPaNIC trial showed that the adverse outcome of early PN in critically ill patients was particularly associated with the amount of protein administered, which the authors ascribed to the inhibitory effect of early protein supplementation on autophagy [29]. Some retrospective studies support the observation that early high protein may be harmful [7,30], whereas other data point to a beneficial effect of early (<4 days) [31], late (4–7 days) [32] or overall higher protein provision with regard to survival (Table 1).

Of note, an international prospective cohort study in 1172 ICU patients modelled the association between calorie and protein intake during the early

Table 1. Overview of observational studies investigating the effect of varying timing and dose of protein supplementation.

Timing	Author, year	Study design	No. of studied (sub)group	Protein delivery[a] intervention vs. control	Effect of higher dose protein intervention
Early (days 1–3)	Koekkoek, 2019 [1▪]	Retrospective cohort	455	>0.8 vs. <0.8	Decreased 6-month mortality (HR 1.23, 95% CI 1.04–1.46)
	Bendavid, 2019 [2]	Retrospective cohort	2253	0.93 vs. 0.39	Decreased 2-month mortality (adjusted[b] HR 0.83, 95% CI 0.71–0.97)
	De Koning, 2020 [3▪]	Retrospective cohort	89	>1.2 vs. <0.8	Increased 6-month mortality (HR 3.90, 95% CI 1.51–10.12) in nonseptic patients
Late (days 4–7)	Koekkoek, 2019 [1▪]	Retrospective cohort	291; 415	>1.2 vs. <0.8; >1.2 vs. 0.8–1.2	Decreased 6-month mortality (HR 0.62, 95% CI 0.46–0.85); increased 6-month mortality (HR 1.40, 95% CI 1.09–1.79)
	De Koning, 2020 [3▪]	Retrospective cohort	273; 81	>1.2 vs. 0.8–1.2; >1.2 vs. <0.8	Increased 6-month mortality (HR 1.55; 95% CI 1.00[c]–2.39) in septic patients; decreased 6-month mortality (HR 0.38, 95% CI 0.16–0.89) in nonseptic patients
	Van Ruijven, 2022 [4]	Retrospective cohort	2618	≥1.2 vs. <1.2 at day 4	Decreased ICU mortality (adjusted[d] HR 0.49, 95% CI 0.39–0.62) and decreased hospital mortality (adjusted[d] HR 0.48, 95% CI 0.39–0.60)
Overall (varying doses in days 1–15)	Hartl, 2022 [5]	Retrospective cohort using piece-wise exponential additive mixed modelling	16489	<0.8 on day 1–4 & 0.8–1.2 on day 5–11 vs. <0.8 on day 1–11; >1.2 on days 1–11 vs. 0.8–1.2 on day 1-11; 0.8–1.2 on days 1–4 & >1.2 on days 5–11 vs. 0.8–1.2 on day 1-11	Decreased hospital mortality (minimum HR 0.75, 95% CI 0.64–0.87) and increased live hospital discharge (maximum HR 1.98 (95% CI 1.72–2.28)); decreased live hospital discharge[e] (minimum HR 0.31, 95% CI 0.24–0.39); decreased live hospital discharge[e] (minimum HR 0.19, 95% CI 0.15–0.24)
	Matejovic, 2022 [6▪▪]	Prospective cohort using piece-wise exponential additive mixed modelling	1172	0.8–1.2 vs. <0.8 or >1.2; >1.2 irrespective of timing vs. 0.8–1.2 on days 1-15	Higher probability of successful weaning from IMV (maximum HR 2.60, 95% CI 1.09–6.23); lower probability of successful weaning from IMV (minimum HR 0.28, 95% CI 0.12–0.65)

95% CI, 95% confidence interval; HR, hazard ratio; ICU, intensive care unit; IMV, invasive mechanical ventilation.
[a]Protein delivery is expressed as grams of protein per kg body weight per day (g/kg/day).
[b]Adjusted for age, sex, weight, parenteral nutrition, mean delivered calories, mean daily protein received after the first 3 days, administration of vasopressors, SOFA score, year of study, and total hospital stay.
[c]Lower limit of 95% confidence interval is 1.004.
[d]Adjusted for APACHE II score, relative energy provision, BMI, and age.
[e]Results were qualitatively changed by a sensitivity analysis due to the assumption of a standard protein intake after ICU discharge. Without those assumptions, a high protein intake appeared to neither worsen nor improve ICU outcomes.

or later stage of ICU admission and outcomes (weaning from mechanical ventilation and survival) and found harm with protein provision exceeding 1.2 g/kg during at least 15 days [6▪▪]. A significant association was observed between moderate protein intake (0.8–1.2 g/kg) from day 1 to day 15 and earlier weaning from invasive mechanical ventilation, yet not with survival, whereas high protein (>1.2 g/kg) was associated with prolonged mechanical ventilation. Using comparable analysis methods on data from a point prevalence study of nutritional practice in ICU ($n = 16\,489$), Hartl *et al.* [33▪] showed that moderate (0.8–1.2 g/kg/day) late (day 5–11) protein administration was associated with a lower rate of in-hospital death and higher rate of live hospital discharge, whereas high protein administration (>1.2 g/kg/day) was associated with increased mortality, irrespective of disease stage.

Taken together, there are substantially conflicting results regarding the association between timing of protein supplementation and outcome in critical illness. The comparability of these studies is hampered by the different cut-off values that are used to distinguish high, moderate and low protein intake. Moreover, although most observational studies attempt to correct for potential confounders, the possible causality of the observed associations between protein intake and clinical outcomes cannot be established. These discordant findings make it difficult to formulate firm recommendations regarding timing of protein supplementation and large prospective RCTs are required.

Apart from the timing and dose of protein, there is increasing interest in other factors influencing muscle mass and strength in critical illness, such as electrostimulation and early physical exercise [34,35]. Nakamura *et al.* [36▪▪] randomized 117 critically ill patients to receive high (1.5 g/kg/day) or medium (0.8 g/kg/day) protein intake. Sixty patients, evenly distributed amongst both groups also received daily electrical muscle stimulation (EMS). Femoral muscle loss was greater in the medium protein group, although this difference only reached statistical significance in groups who received EMS. However, the high protein formula contained whey protein, as opposed to soy in the medium protein group, possibly influencing the results due to differing leucine contents (an important anabolic stimulus) and its subsequent different effects on myofibrillar synthesis. In addition, the intervention did not result in differences in patient centred outcomes such as activities of daily living or quality of life at hospital discharge.

In a similar intervention in a neurocritical care setting, high protein intake (1.5 g/kg/day) combined with EMS of the quadriceps muscle compared to usual care (0.9 g/kg/day) resulted in less muscle atrophy (6.5% vs. 12.5%, $P = 0.01$), yet no difference in lower extremity mobility was found [37]. It should be noted however that muscle function may be difficult to measure in neurologically impaired patients. Increasing the amount of activated muscle may improve functional outcomes. To investigate this, Kagan *et al.* [38] performed a randomized pilot trial in 41 patients comparing three groups: conventional physiotherapy, cycle ergometry with standard EN, and cycle ergometry with protein-enriched EN. They found no differences with regard to duration of mechanical ventilation, length of ICU or hospital stay, ICU mortality, or re-intubation rate, which might be attributed to the small sample size. Moreover, they did not study long-term functional outcomes, as opposed to de Azevedo *et al.* [39▪▪] who studied 87 patients receiving high protein and early exercise and 94 patients receiving routine nutrition and physiotherapy in a randomized controlled trial. They found a significant difference in their primary endpoint, the physical component summary (PCS) of the Short Form Survey (SF-36), at three and six months favouring the intervention group. Remarkably, they found a difference in mortality (33 vs. 54%, $P = 0.005$) at six months, which has not previously been established in studies of protein administration and exercise in ICU and is likely to represent a Type I error relating to the very high mortality rates in both groups (31% and 52%).

Overall, the available literature suggests that muscle activation combined with protein administration may be more effective at attenuating muscle loss and positively influencing long-term functional outcomes. Larger prospective studies to confirm these preliminary observations are needed.

WHOLE PROTEIN OR INDIVIDUAL AMINO ACIDS?

Though international critical care nutrition guidelines recommend protein supplementation, they do not specify what type of protein should be provided or whether there is a role for supplementation of individual amino acids in critical illness. Whether supplementation with individual amino acids, rather than whole protein, can overcome the anabolic resistance of muscle and improve outcomes in critical illness remains uncertain. The safety of such an approach is also unclear, given that administration of large nonphysiological doses of amino acids may theoretically suppress autophagy, increase ureagenesis and supply precursors of toxic neuromediators. One of the largest RCTs (the Nephro-Protective trial, $n = 474$) [40] of amino acid

supplementation in critically ill patients (up to 100 g/day of intravenous amino acids vs. standard care) showed that amino acid supplementation did not preserve renal function and resulted in significantly higher serum urea levels. Previous evidence also suggests increased mortality with the use of intravenous glutamine in ICU patients with multiorgan failure [41] and caution is warranted.

The branched chain amino acid leucine is one of the most potent stimulators of muscle protein synthesis and acts via stimulation of the mammalian target of rapamycin (mTOR) pathway [42▪]. Its metabolite, β-hydroxy-β-methylbutyrate (HMB), also stimulates muscle synthesis via the mTOR pathway but, in addition, attenuates proteasome pathways that lead to muscle protein catabolism. HMB has been found to increase muscle mass and strength in a variety of clinical conditions including cancer cachexia, end-stage renal failure, HIV infection and older age [43]. There has been only one recent study of leucine supplementation [44▪] and three recent studies of HMB supplementation in critical illness [18▪,19▪,45]. Wandrag *et al.* [44▪] conducted a feasibility study of leucine-enriched amino acid supplementation in critically ill trauma patients but reported difficulties with recruitment, administration of the supplement five times per day, and assessment of physiological outcome measures including muscle thickness by ultrasound and nitrogen balance.

A single centre open-label RCT in Japan of 88 participants evaluated the effect of HMB (total 3 g/day) in combination with arginine and glutamine from day 2 of ICU admission on femoral muscle volume loss measured by CT [18▪]. All patients received early rehabilitation and electrical muscle stimulation daily. There was no difference in the primary outcome at day 10 of ICU admission, but any effect of HMB is difficult to elucidate in this trial because HMB was administered in conjunction with arginine and glutamine. Supinski *et al.* [45] randomised 83 mechanically ventilated patients in a blinded fashion to one of four groups for 10 days: HMB (3 g/day), HMB (3 g/day) and the omega-3 fatty acid eicosapentaenoic acid, eicosapentaenoic acid alone, or control. There was no difference between groups in diaphragm strength, quadriceps strength or ultrasound-derived diaphragm thickness.

A smaller partially blinded single-centre RCT [19▪] randomised 30 mechanically ventilated patients to HMB (3 g/day) or placebo for a longer period of time (up to 30 days). There was no difference in the primary outcome of ultrasound-derived rectus femoris muscle loss between days 4 and 15. However, net protein breakdown as measured by amino acid tracer methodology was reduced in the HMB intervention group. Further large studies of HMB supplementation in critical illness are needed and these should evaluate HMB in the absence of other supplements, continue supplementation into the recovery phase after ICU discharge when anabolic resistance may be reduced [46] and evaluate physiological outcomes to further improve our mechanistic understanding.

There have been limited recent studies of supplementation with other amino acids in critical illness. A large multicentre double-blind RCT has evaluated glutamine supplementation in burned patients [47▪▪], given that several small single-centre RCTs have suggested reduced mortality and length of hospital stay with glutamine supplementation and international nutrition guidelines for major burns recommend glutamine supplementation. A total of 1029 patients were randomised to enteral glutamine (0.5 g/kg/day) or placebo. Glutamine supplementation did not reduce the time to discharge alive from hospital. Although this study was affected by slow recruitment, leading to alteration of the sample size and primary outcome, the findings suggest that routine glutamine supplementation in burned patients should be reconsidered.

There has also been recent interest in the conditionally essential amino acid glycine, which appears to have anti-inflammatory effects and restores the anabolic sensitivity of skeletal muscle to leucine in animal models of muscle wasting including sepsis [48]. A recent randomised double-blind crossover trial of 36 malnourished chronic haemodialysis patients demonstrated that glycine supplementation (7 g/day) improved fat-free mass index as measured by bioelectrical impedance analysis when compared with branched chain amino acid supplementation [49] and studies in ICU patients are ongoing (ACTRN12618000409279).

CONCLUSION

Adequate protein provision may be important to prevent muscle loss in critically ill patients and improve functional outcomes. However, the optimal dose of protein remains uncertain and is currently subject to large clinical trials. There is no strong evidence that ICU patients should receive supplementation with any specific amino acids. Future studies of whole protein or amino acid supplementation should initially test one supplement at a time, instead of multiple agents in conjunction. Furthermore, there is an urgent need for mechanistic studies of protein metabolism, muscle protein kinetics and muscle pathophysiology in critical illness to inform the selection of protein type, dose and timing in future large clinical trials. Such

mechanistic studies will also provide vital information about the best methods to monitor muscle loss at the bedside. Lastly, future clinical trials should focus on protein supplementation in conjunction with exercise in the ICU or in the recovery phase of critical illness after ICU discharge, when muscle anabolic resistance decreases and patient mobility increases.

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Conflicts of interest

There are no conflicts of interest.

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