Fundamental determinants of protein requirements in the ICU

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Purpose of review
Currently, feeding the ICU patient is highly discussed. Energy feeding has been the topic of randomized studies, but protein feeding has not. Study results are contradictory on early feeding; however, little is known about early protein requirement. What is this protein requirement based on, therefore what are the fundamental determinants?

Recent findings
Recent studies have addressed the importance of protein feeding and/or muscle (protein) wasting in critically ill patients. Targeted feeding has been shown to improve protein balance in one study, and infection rate in one study. Low muscle mass that is already present during ICU admission has been shown to be related to higher mortality, in two studies. Four studies have related muscle wasting to (protein) feeding strategies with very diverse results: Two small studies have reported no advantage [$n = 15$, computed tomography] or negative impact ($n = 62$, ultrasound, 50% sepsis patients) of protein on muscle wasting. Two studies, one small ($n = 33$, computed tomography) and one very large ($n = 1372$, Subjective Global Assessment), have reported a positive impact of (early) feeding on muscle wasting.

Summary
Fundamental to adequate protein feeding in critically ill patients, at least 1.2 g protein/kg per day, is targeted energy feeding using indirect calorimetry. The level of protein requirement is related to fat free mass or muscle mass, which makes sex and BMI also relevant. Targeted early protein feeding is found to improve short-term outcome, reduction of muscle wasting and hospital mortality. Long-term outcome of protein feeding has not been studied. However, targeted protein feeding may be harmful in sepsis patients. Up to now, we lack biomarkers that provide caregivers with an instrument to increase protein feeding up to the individual protein requirement of the critically ill patient.

Keywords
critically ill, muscle mass, protein dosing, protein needs

INTRODUCTION

Considering the adult patient at the ICU, there is still considerable controversy as to what, how, how much and when to feed this patient. In general, the discussion has concerned the amount of energy, which for many practitioners appears to be identical to the amount of 'nutrition' needed. For energy itself, it is becoming more and more clear that targeted feeding of the patient, by measuring the actual energy expenditure of the patient, is essential to optimize patient care [1]. Most practitioners working in the ICU will be aware that muscle wasting is present in critically ill patients. However, muscle wasting may not always be recognized as the result of a negative protein balance that may be related to the actual amount of protein that is supplied with enteral or parenteral nutrition to the patient. Admittedly, this is an oversimplification of the situation.

In clinical practice, the protein needs are obtained from national or international guidelines

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KEY POINTS

- Understanding of fundamental determinants of protein requirements in critically ill patients is weak, but guidelines of 1.2 g protein/kg per day are currently supported.
- Muscle mass is important for both short-term and long-term outcome in critically ill patients and can be modified by protein feeding.
- Tipping the delicate balance between wasting that is beneficial for short-term survival or fatal to long-term physical function remains a matter of debate.
- There are no data to support a lower early protein intake; there are data to support a lower early energy intake.
- Fundamental determinants of early protein feeding should be biomarkers, functional markers and outcome based.

[2–4], rather than biomarkers obtained from the patient. The usual expression for protein requirements is in gram per kilogram body weight per day. There are no specifications concerning sex, age, BMI, severity of illness and timing during the course of disease. The ASPEN guideline does in fact discriminate in obese and nonobese patients concerning protein requirement. The actual evidence base for protein requirements in the ICU, and in fact in any other healthcare setting, is very weak. There is not a single randomized controlled trial based on different levels of protein intake and relevant outcome measure.

WHAT IS THE BASIS OF PROTEIN REQUIREMENTS (IN HEALTH)?

Let us consider what the actual basis for the protein requirement is. Historically, the nitrogen balance test has been used in healthy adults to guide us concerning the level of protein that is required for maintenance of 'structure and function' [5]. When the diet is protein free, body protein is lost from the body and the nitrogen balance is negative. The minimum amount of protein needed is the amount of protein needed to compensate the loss of body protein. However, when this amount of protein is consumed, nitrogen balance is not achieved. This is due to an inefficient use of dietary proteins, due to an 'adaptive' increase in amino acid oxidation. Current recommendations for healthy people are based on linear regression analysis of individual nitrogen balance data with a large variation in protein intake. The well tolerated level of protein intake is 0.83 g protein/kg body weight per day [5,6]. The nitrogen balance method is not ideal, the actual measurement of nitrogen losses is not easy and application of correction factors (e.g. for nitrogen loss from skin) may not be adequate and sometimes surprisingly positive nitrogen balances in adults are observed [5,7]. More importantly, we do not know whether overall zero nitrogen balance is actually related to health; it is mainly a required condition for health.

Two further aspects need to be addressed: diurnal protein cycling and protein turnover. The normal diurnal variation in protein balance consists of a postabsorptive period with negative protein balance and a feeding period with a positive protein balance [7]. Both diurnal cycling and nitrogen losses decrease and increase with protein intake [7]. The concept of the anabolic threshold is related to cycling and can be used to optimize protein intake [8]. Diurnal protein cycling is of course part of whole body protein turnover each day, although the most critically ill are continuously fed. Body protein is in a constant state of protein turnover, with protein synthesis and protein breakdown levels estimated to be in the order of 350 g/day [9]. Notably, this is 3.5–5 times a normal daily protein intake. A reference man of 70 kg contains 10 kg of protein, which is replaced in 28 days. This is an overall value, as all individual functional proteins are synthesized by transcription and translation in very different rates. Protein turnover ensures a certain adaptability to environmental and health threats. Some proteins contain structural mistakes that compromise protein function. The level of protein turnover or cycling that is needed for maintenance of good health is unknown.

APPLICATION TO CRITICALLY ILL PATIENTS

When protein supply is suboptimal, body protein is lost from the body. This is an adaptation to starvation for survival, with lower body protein mass causing lower losses and requirement. The level of protein turnover that supports adaptability, and protects against subclinical and clinical features of malnutrition and illness, is unknown. Survival is particularly at risk in the ICU. In critically ill patients, the acute response may require redistribution of available amino acids. Acute phase proteins and immune system may benefit from muscle protein breakdown. Any misfit in amino acid mixture between protein breakdown and protein synthesis will cause an increased amino acid drain and excessive muscle wasting. In a critically ill patient, the tipping point between the acute

benefit of adaptability (protein function) and long-term harm (muscle wasting, weakness and decreased functionality) is currently unknown. Long-term consequences are well documented and harm to functionality, such as 6 min walk test, is only regained partly after 1 or even 5 years [10].

The ICU contains patients with a large variation in severity of illness and stages of disease. But no specified protein requirements are available. Patients can be categorized into acute, chronic and recovery phase [11]. Currently, the literature is mainly confused about the early acute/chronic phase, in practical terms the first week of admission to ICU. First, the patient has to be stabilized and diagnosed; nutrition is considered a secondary requirement or no requirement at all. Critically ill patients around the world have protein intakes of 60% of target for up to 12 days [12]. Acutely after surgery, protein turnover is increased and body protein is lost [13]. Protein lost in critically ill trauma and sepsis patients were observed to be 2 kg (16%) in 10 days for the 0.9 g/kg protein intake level but only half (8%) at 1.2 g/kg [14]. And, in severe trauma patients, it was 0.5 kg in 8 days at zero protein intake and half by any investigated protein intake level [15]. Therefore, early protein requirement should at least be considered.

TIPPING THE BALANCE, AUTOPHAGY AND SEPSIS

The higher level of protein turnover would be expected to be in part due to increased autophagy, especially when body protein structures have been compromised by trauma, surgery or metabolic disease. Autophagy is considered a housekeeping system to remove dysfunctional and toxic protein and complete cellular structures [16,17]. In a critically ill animal model, fasting versus feeding resulted in catabolism, functional autophagy, improved maintenance of cell integrity and protection of organ function [18]. This may suggest that protein feeding inhibits protein breakdown, which hampers autophagy when it is needed most. This particularly underlines the need to understand the balance between benefit now and long-term harm.

A more complete parenteral nutrition formula has been shown to normalize protein turnover by high energy and protein (1.5 g/kg) supply in gastrointestinal surgery patients [19]. Protein breakdown increased by 60% when only glucose was supplied, while with a protein intake of 1 g/kg, it was 30%. In sepsis patients, protein synthesis was not different and protein breakdown was 160% higher than the level in healthy controls with a 1 kcal/kg.h parenteral feeding [20]. Septic patients may have such an increase in protein breakdown that the large amount of protein needed will do little benefit while doing substantial harm to the autophagy process. To increase protein supply in order to obtain zero nitrogen balance appears unrealistic and possibly harmful. Higher than 2.0 g/kg has been advised for critically ill patients [21], although others have suggested trophic or low feeding or late supplemental parenteral nutrition as discussed earlier [22].

WHAT CAN WE LEARN FROM NONCRITICALLY ILL?

Protein requirements in older adults or the elderly are suggested to be higher than the current recommendation of 0.83 g/kg [23]. A serving of 30 g lean meat protein is sufficient to have an optimal muscle protein synthesis response in the elderly, which is equal to that in the young because muscle protein insulin resistance is overcome [24]. Here, muscle protein synthesis is used as a functional indicator of the higher protein needs. Recently, we found the optimal level of protein intake in obese older adults during a 13-week course of voluntary weight loss to be 1.2 g/kg, based on muscle mass accretion during this challenge period [25]. Here, muscle mass accretion is used to obtain outcome-based protein needs. Thus, we need biomarkers, functional parameters and outcome-based research, rather than just nitrogen balances.

RECENT STUDIES

Some recent studies have addressed either protein feeding or muscle (protein) wasting or both in critically ill patients.

Berg *et al.* [9] have shown that targeted (protein) feeding improves protein balance. Two levels of total parenteral feeding (100 and 50% of measured energy expenditure) are compared. Provision of full feeding significantly improved the negative protein balance observed by 50%, see Fig. 1. The protein dose was 1.07 g/kg/day for 100% and 0.53 g/kg/day for the 50% feeding level. It was an acute study of only 48 h; therefore, adaptive mechanisms may be missed. Thus, full targeted feeding does provide means to reduce muscle (protein) wasting in the ICU.

Heidegger *et al.* [26▪▪] have shown in a randomized controlled trial that supplemental parenteral nutrition on days 4–8 improved the rate of nosocomial infections, when based upon targeted feeding using indirect calorimetry ($n = 305$). Patients included had energy intake of less than 60% of energy target. Indirect calorimetry was performed late on day 3, and supplemental parenteral nutrition

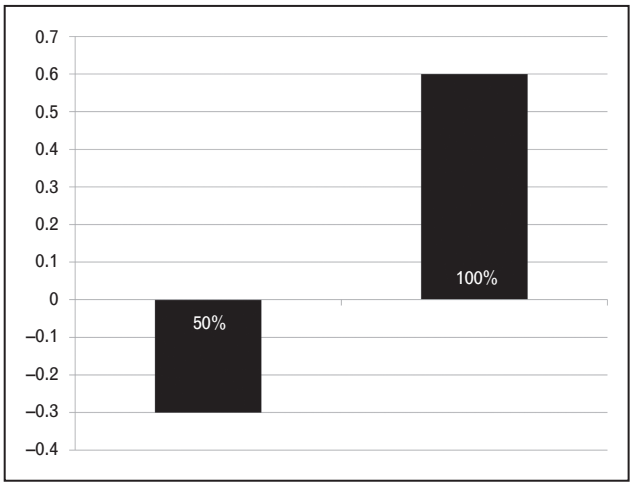

FIGURE 1. Whole body protein balance with 50 or 100% of feeding target, expressed as mg leucine per kg per hour.

started early day 4 up to energy target. Using individual energy targets and adequate protein supply of 1.2 g/kg improved primary outcome, similar to the TICACOS study [27] and with some discussion [28]. As the control group received 0.8 g/kg, although internationally a protein intake of 0.6 g/kg or less is quite common [12], a larger effect may have been possible. Targeted feeding protects patients from overfeeding, which may have contributed to infection rate in other studies [27,29], although protein feeding may still have to be improved further [30].

We have suggested earlier that protein intake is not a one size fits all [31▪▪]. Using protein intake per kilogram fat-free mass as a reference, we have proposed adjusted body weight for underweight and obese critically ill patients. New studies have shown that low muscle mass during admission to ICU was associated with higher mortality. Moisey *et al.* [32▪▪] showed ($n = 149$) that muscle mass assessed by computed tomography (CT) scan at admission is associated with mortality in sarcopenic elderly. As sarcopenic elderly have been shown to have worse outcome before, it is interesting to see whether for the critically ill this is true for sarcopenic young patients. Weijs *et al.* [33▪▪] have shown that this effect is not restricted to old age. The effect of low muscle mass on mortality is a specific mass effect, that is independent of sex, age, BMI, APACHE II score and diagnosis. Stepwise regression analysis has shown that low muscle mass is most predictive of mortality, with APACHE II score as a significant second factor [33▪▪]. When low muscle mass is so predictive, it may also be an important determinant of protein requirement. Future studies will have to show whether increased protein supply improves outcome, especially in low muscle critically ill patients.

Because low muscle predicts mortality, it is important to know whether muscle wasting in critically ill patients can be decreased by a feeding strategy. Casaer *et al.* [34] have shown in a very small substudy of the large randomized controlled trial EPaNIC that early supplemental parenteral nutrition does not prevent muscle wasting. They conducted repeated femoral CT scans on median day 2 and day 9, but only in 10 individuals from early PN and five individuals from late PN group [29,34]. Protein intake of the group is unclear [34]. It is clear that early protein intake is increased with early PN in the EPaNIC trial, however not meeting current guidelines [29]. Up to day 3 protein intake is extremely low in both groups. In the early PN group, protein intake ranges 0.8–0.9 g/kg on days 4–9, whereas in the late PN group, protein intake is extremely low. Therefore, this study showed that muscle wasting during the first week in the ICU cannot be adequately treated with a protein level of 0.8–0.9 g/kg starting from day 4. Judging from energy intake, the protein intake differences between groups were rather small [34]. EPaNIC has used estimated energy targets, which are known for large errors compared with indirect calorimetry [35]. The 10 patients in the early PN group can be overestimated and overfed, while the five patients in the late PN group were not at risk of overfeeding. With overfeeding, the increase in intramuscular fat with early PN is not a surprising finding.

In a post-hoc observational analysis, Casaer *et al.* [36] has shown that, irrespective of the route of administration, the level of energy and protein provided during critical illness will worsen early ICU discharge. Energy intake levels of more than 50% of estimated energy target (all early PN, <20% of patients) have worse outcome on day 3, of more than 90% at day 5 and no effect on day 7. The high energy intakes at day 3 are odd, as PN only started at day 3 and caloric target was supposed to be met at day 4. From another analysis, it becomes clear that the high glucose intake does not affect outcome, whereas higher protein intake at day 3 (only) does. Protein targets did not exist; therefore, intakes were expressed as percentage of estimated energy target. The estimated energy target is highly inaccurate [35]. Protein feeding is probably highly correlated to energy feeding, and therefore also a possible explanation for the finding that protein feeding did harm outcome.

Puthucheary *et al.* [37▪▪] have shown that the level of protein feeding does affect muscle wasting in a group of critically ill patients, of whom 50% were sepsis patients. This small ($n = 62$), prospective, descriptive study reports on rectus femoris muscle

(ultrasound cross-sectional area) wasting in critical illness. Muscle decreased by 18% over 10 days, and the decline appeared linear. Muscle wasting was more severe in multiorgan than in single-organ failure patients. This study adds some mechanistic insight into muscle wasting by application of different methodology [37▪▪]. Nutrition was not the focus of this study. However, protein intake was claimed to adversely affect muscle loss. The authors have used two statistical approaches, linear and logistic regression analysis. Therefore, twice they have investigated the effect of 50 variables on a total number of 62 data points. Then, the variable with a P value of less than 0.1 ($n = 17$) has been included into a multivariate analysis, which would be 17 variables into one analysis with 62 data points. This is a challenge. Then, protein appears in the linear regression model, but not in the logistic regression model. There is no information on the nutritional policy, body weight, BMI, protein intake in g/day or g/kg.day. We have shown that protein-targeted feeding improved outcome [38,39]. Unpublished results, however, show that the reverse outcome is obtained in the sepsis subgroup (Fig. 2). In the study by Puthucheary *et al.* [37▪▪], 50% of the patients were admitted with sepsis. Targeted protein feeding in sepsis patients may be detrimental, unless a basic understanding of protein requirements can provide a more (sepsis) specific protein target.

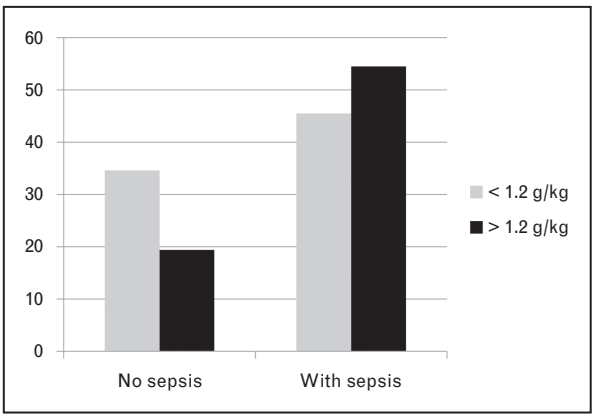

FIGURE 2. Percentage hospital mortality for patients with admission diagnosis sepsis or not. Patients were selected ($n = 493$) from the database used for reference [39], using a maximum energy intake on day 4 of admission of 110% of indirect calorimetry (in order to avoid overfeeding). Early protein intake at day 4 of admission was either lower than 1.2 g protein/kg per day (grey bars), or higher than 1.2 g protein/kg per day (black bars). Reaching the protein target of 1.2 g/kg in the no sepsis group showed a significantly lower hospital mortality ($P < 0.012$); however, in sepsis patients, there was no advantage.

Doig *et al.* [40▪▪] have shown in a large ($N = 1372$) randomized controlled trial that early PN did not affect 60-day mortality; however, early PN significantly decreased muscle and fat wasting [Subjective Global Assessment (SGA)] over the first 7 days of ICU stay. Invasive mechanical ventilation was significantly improved by early PN. Quality of life (RAND36) was significantly improved at 60 days, but the physical component score was not. Therefore, positive effects were found by early feeding on wasting and quality of life, but did not affect mortality. The trial used estimated energy targets, and no protein targets. Protein intake reached a level of 50–60 g/day in the early PN group by day 3, but only by day 7 in the standard care group. In a group of patients with a mean BMI of 28 kg/m^2, 50–60 g/day remains below the current recommendations.

Braunschweig *et al.* [41▪▪] showed ($n = 33$) the use of CT scans with a small descriptive study for longitudinal assessment of muscle mass at L3 cross-sectional area, with an interval of 10 days. Energy needs were estimated. Protein intake was 0.55 g/kg, which is frequently observed but insufficient considering current guidelines. It is suggested that an increase in percentage of energy needs received is associated with 0.024 cm^2 muscle mass preserved. Potentially, an increase in percentage of energy needs received from 40 to 80% may result in 1 cm^2 muscle mass gain. However, firm conclusions cannot be drawn. Muscle wasting in women was 11% (11 cm^2) and in men was 4% (6 cm^2). Earlier, we found targeted protein feeding to be most effective in women [38].

HOW DO THESE NEW STUDIES ADD TO OUR EXISTING KNOWLEDGE?

Currently, our basic understanding of protein requirements for critically ill and certainly for specific subgroups is very weak. The discussion about early feeding of the critically ill patient is fairly extreme. Recent evidence mainly suggests that both extreme views, either very early or very late in the first week of admission, should be modified. An important development is the consideration of body composition, that is muscle mass. This intermediate endpoint may both relate to mortality and long-term functional outcome, although it may be modified by (protein) nutritional therapy. Studies evaluating nutritional therapy should be based on indirect calorimetry, as otherwise the level of feeding cannot be related to the individual patient and cannot be a targeted approach. As protein feeding has not been studied directly in a randomized trial or independently of energy,

we are still at the beginning of understanding fundamental determinants of protein requirements in critically ill patients.

CONCLUSION

Up to now, protein requirements of critically ill patients are not well understood or studied, but guidelines recommending 1.2 g protein/kg per day are supported. Attempts have been made to improve nutritional care of the critically ill patient. However, most studies have been trial-and-error approaches. Our improvements in clinical practice have been shown to increase protein intake as well as outcome [42,43]. However, high protein feeding may also be harmful when provided to sepsis patients too early. Therefore, the delicate balance between early and high enough to keep the muscle, and late and low enough to be safe will have to be studied in much more detail. There are no data to support a lower early protein intake; there are data to support a lower early energy intake. It is clear that protein feeding should not only improve mortality [44] but also reduce muscle wasting, weakness, and thereby improve long-term functionality of intensive care survivors.

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Conflicts of interest

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