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A Crash Course in Muscle Wasting, Protein Requirements and Long-term Outcomes in Critically Ill Patients

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Introduction

For the last 20 years, research in nutrition for critically ill patients has focused on energy provision and immuno-nutrients and, to date, there are no randomised, prospective trials investigating the optimal protein intake for this group. However, the suggestion that inadequate protein provision may be responsible for the failure of recent, large randomised controlled trials to show a benefit from nutritional interventions has increased interest in this nutrient. Further to this, newer techniques to assess muscle wasting and protein turnover, such as muscle ultrasound, CT and stable isotopes, have enabled more detailed studies to be undertaken on the effect that critical illness and, indeed, nutrient provision has on lean body mass. As the number of patients surviving sepsis and critical illness increases, so too has the number discharged to a rehabilitation facility and home with some degree of functional disability.[1] Studies investigating muscle wasting are, therefore, becoming more important as we search for the most appropriate intervention to reduce the functional disability associated with a prolonged stay in the intensive care unit (ICU).

This article will briefly discuss the recent findings relating to ICU acquired weakness, the pathophysiology of muscle wasting and the current evidence surrounding protein requirements in critically ill adults.

ICU acquired weakness

It is well-known that patients who survive critical illness experience significant muscle weakness leading to physical disability. This weakness, termed 'ICU acquired weakness' (IAW) has been reported in 50 per cent of patients receiving mechanical ventilation for more than seven days.[2] Perhaps obvious, IAW is associated with delayed weaning from mechanical ventilation, increased length of ICU and hospital stay, increased healthcare costs and is an independent risk factor for death.[3] Long-term follow-up studies have shown that this weakness and disability is still present one year post discharge from the ICU[4] and even up to five years.[5]

Reducing the impact of IAW has been at the forefront of ICU care over recent years, particularly with the publication of the NICE guidelines for rehabilitation after critical illness, which were published in 2009.[6] Indeed, large randomised controlled trials investigating the effects of nutrition in critically ill patients[7] are now including long-term function and quality of life (QoL) outcomes rather than solely focusing on mortality, time on ventilation and length of stay, which are unlikely to be affected by such interventions.

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A major contributor to IAW is loss of lean body mass, an unfortunate, but inevitable outcome from a prolonged ICU admission. Although multifactorial in its origin[3] (**Table One**), inadequate nutritional support almost certainly contributes. Currently data are positive for in ICU based rehabilitation programmes,[8, 9] but only one post-ICU study has shown a benefit.[10] None have included an aspect of nutrition. The recently published sub-analysis of the large EDEN trial reported no significant difference in physical or cognitive outcomes between patients receiving trophic or full feeding one year post discharge from the ICU.[7] No specific rehabilitation programme was included. Although no statistical difference was seen in these outcomes, one could controversially argue that the treatment effect for the six-minute walk test and four-meter timed walk speed were heavily in favour of the full feeding group (63% [25%] vs 70% [24%]; p=0.136). Overall, caution needs to be taken when interpreting these results due to the specific population studied and our current poor understanding of the relationship between protein balance, muscle wasting and feeding during early critical illness.

Table One: Factor Contributing to ICU-Acquired Weakness

- Inflammation (severity and duration)
- Use of neuromuscular-blocking agents
- Corticosteriod use
- Hyperglycaemia
- Hypoalbuminemia
- Immobilisation

What do we know about protein balance and muscle wasting in critical illness?

It is well documented that critically ill patients can lose up to two per cent of their lean body mass per day during an ICU admission.[11, 12] Although survivors of critical illness have been shown to regain the weight lost, a large percentage of this is fat rather than muscle, which has implications for functional recovery.[4] The pathophysiology of muscle wasting in this population is still poorly understood. However, recent translational research has provided further important insights. One UK study (MUSCLE-UK) aiming to evaluate and characterise the trajectory of muscle wasting in critically ill adults found that it occurs early and rapidly during the first week of critical illness and is more severe in patients with multiple organ failures, rather than single organ failure.[11] In this group of patients, muscle wasting occurred despite the provision of nutrition and, surprisingly, was higher in patients receiving more protein. They also found that while protein synthesis returns to the levels of a healthy, fed control at the end of the first week of critical illness, net protein catabolism remains increased. Similarly, a subanalysis of the EPaNIC trial, which investigated pathways relating to protein catabolism, also found that muscle wasting occurred early on in critical illness and this was irrespective of the patients receiving early or late parenteral nutrition.[13] Protein intake was not assessed separately.

These are all important findings in this area and will certainly lead to further trials investigating methods to reduce the catabolic response. One such method that has been hypothesised is bolus feeding rather than the usual continuous feeding regimen.[11] The basis for this hypothesis stems from data in healthy individuals[14, 15] and elderly women,[16] indicating that muscle protein synthesis is best stimulated with 'pulsed' administration of amino acids. We eagerly await the results of such a trial in critically ill patients.

Why might early feeding not stop catabolism?

There are several pathways involved in protein breakdown, including the ubiqutone-proteosome pathway, which has been well documented and the autophagy-lysosome pathway.[17] If you have kept up with the recent publications on nutrition and critical illness, you would have most certainly heard the term autophagy. Autophagy is not an easy concept to understand, but its importance in the muscle wasting process has become evident over recent years. Autophagy can be most simply explained as a process whereby damaged organelles, protein aggregates and intracellular pathogens are eliminated from cells. This process is essential for the cells to survive.[17, 18]

The integrity of muscle protein is largely regulated by autophagy, meaning that any interruption to this important process will affect muscle wasting. Nutrients, in particular amino acids, are a powerful inhibitor of autophagy, while starvation is a powerful activator.[17, 18] Indeed, skeletal muscle biopsies of critically ill patients have shown signs of insufficiently activated autophagy in those receiving enteral nutrition, parenteral nutrition or both.[19, 20]

Whilst autophagy may go someway to explaining the relationship between early feeding and muscle wasting, further research is still warranted. Furthermore, studies are yet to investigate autophagy after the first week of critical illness and these studies have the potential to influence interventions which may impact recovery.

How much protein should we be giving?

Should we be giving less protein given the results of the MUSCLE-UK Study? Not quite. Further research, with larger numbers of patients is certainly needed to determine the relevance of the above findings, but reducing protein intakes at this point would prove premature and likely detrimental to an already significantly underfed group.

One of the major aims of providing nutrition support to critically ill patients is to attenuate skeletal muscle wasting in order to reduce functional disability. However, conclusive data on the most appropriate feeding regimen are still lacking and available data are often conflicting. Further to this are the frequent barriers encountered in the ICU environment which prevent the prescribed nutrition from being received. International Guidelines for nutrition in critically ill patients differ slightly in their recommendations for protein intakes, but suggest somewhere between 1.2 g/kg and 2.5 g/kg depending on the patient group (**Table Two**).[21, 22, 23, 24]

Table Two: Recommendations for Protein Targets in Specific Patient Groups

Patient Group	Protein Target
General ICU	1.2-1.5 g/kg
Continuous renal replacement therapy	1.5-1.7 g/kg
Burns	1.5-2.0 g/kg
Trauma	1.3-1.5 g/kg
Obese	2.0-2.5 g/kg (ideal body weight)

Given the absence of randomised controlled trials investigating the optimal protein provision during critical illness, the guideline recommendations are based on several observational studies. Indeed, a recent systematic review of appropriate protein provision in critical illness is based solely on observational studies. The authors of this review suggest that 2.0-2.5 g/kg may be optimum for this patient group but acknowledge the limitations of the studies included, and strongly recommend well designed trials investigating this issue.[25]

Despite these recommendations, the International Nutrition Survey, a worldwide survey of nutritional practices in the ICU, continues to show that patients are receiving well below these recommendations, with patients receiving, on average, 0.67 g/kg/day[26] (**Table Three**).

Table Three: Barriers to Inadequate Provision of Protein

- Low protein content of commercially available enteral and parenteral preparations
- Poor adherence to local feeding protocols
  - Inappropriate management of gastric residual volumes
- Feed interruptions
  - Airway management
  - Theatre
  - Other ICU procedures
- Lack of feeding access
- Team knowledge and attitude to feeding

Indeed, several large, randomised controlled trials investigating the impact of nutrition in this group of patients also fall far short of recommended levels which may partly explain their failure to show improved outcomes.[27, 28] Experts in ICU nutrition have also pointed out that, the trials which have delivered 1.0 g/kg or more of protein, have shown a benefit on outcome,[29, 30, 31] which would support findings in observational studies on protein intake.[32, 33] Adding to this are the results of the OMEGA trial where there was a significant difference in mortality (the lowest ever recorded mortality in a group of patients with acute lung injury in fact) between the control and intervention groups which favoured the control group.[34] The very large difference in protein between the control and intervention feed has been cited a potential factor in this result.[29]

The issue of universally low provision of protein (and energy) through enteral feeding is being addressed in the PEP-uP trial.[35] Although the feasibility study has shown only modest increases in protein provision, the larger study will aim to address the issues surrounding implementation of the protocol. Furthermore, it is imperative that medical nutrition companies work to improve the protein content of commercially available enteral and parenteral feed preparations to assist in meeting the unique needs of ICU patients.

Are the recommendations the same for everyone?

As with all aspects of care in the ICU, the heterogeneity of the patient population will mean that some degree of individualisation is required. Although the evidence is clearly lacking, additional protein is commonly provided to patients with burns (1.5-2.0 g/kg/day),[36] those on continuous renal replacement therapy (1.5-1.7 g/kg/day)[37] and trauma patients (1.3-1.5 g/kg/day).[22] However, most recently, it has been highlighted that patients with a low 'nutritional reserve' or poor pre-illness nutritional status may benefit from more aggressive nutritional support, including protein provision.[26] In fact, it was found that providing an additional 30 g protein per day improves mortality. This outcome was only seen in patients with a BMI less than 25 and more than 35, which may be an indication that the proportion of lean body mass is an important factor when determining feeding regimens. This finding supports recent recommendations that we should be aiming for 2.0-2.5 g/kg of ideal body weight for obese patients.[38]

Conclusions

Recent advances in techniques to measure muscle wasting and protein turnover in critically ill patients has provided us with valuable insights into the way these patients may utilise fuels, in particular, protein. As new evidence emerges, we need to remain flexible to changes in nutritional interventions but, ultimately, we need to be advocating and participating in research that helps to define the protein targets for these patients both within and post-ICU stay and which aim to optimise long-term recovery. In the meantime, guideline amounts for provision of protein in critically ill adults should be used in practice.

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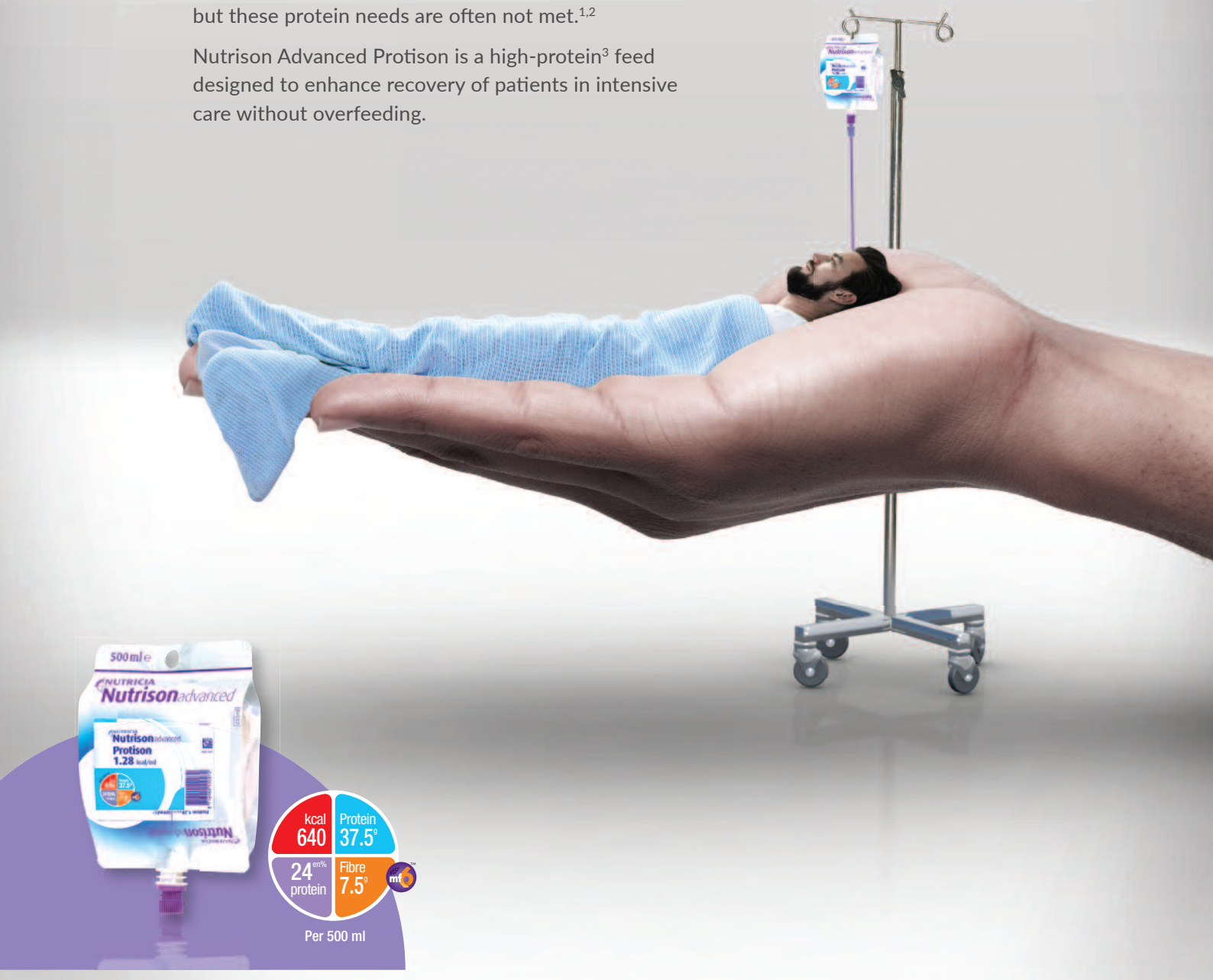

* Total Energy Expenditure (TEE) + 10%

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