The disconnect between nutrition guidelines and evidence: how much protein should I prescribe to this critically ill patient?

Adam M Deane, Sandra L Peake and Marianne J Chapman

Nutritional therapy is an essential part of routine care for critically ill patients;[1-3] however, the guidelines are rarely based on prospective blinded randomised clinical trials of adequate size.[4] Accordingly, practice is informed by lesser grades of evidence and opinion.

In 2011, we were awarded project grants from the Royal Adelaide Hospital and the Australian and New Zealand College of Anaesthetists to conduct the Augmented versus Routine Approach to Giving Energy Trial (TARGET),[5] which was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG). We established that it was possible to increase calorie delivery by about 50% in a blinded fashion while maintaining similar protein delivery between intervention and standard care groups. We therefore planned a larger blinded, parallel group, randomised clinical trial to determine whether augmented enteral calorie provision to critically ill patients, when compared with standard care, reduces mortality by about 4%,[6,7] and 4000 patients were recruited within 18 months. We believe that TARGET sets a new internal validity standard for large critical care nutrition trials and establishes the capacity of the Australian and New Zealand intensive care community to undertake and promptly complete such trials to inform international practice.

TARGET will only provide information about calorie delivery. There remains many other equally important questions related to nutritional therapy during critical illness for which there is very little high-quality evidence.[8] Recently released critical care nutrition guidelines, endorsed by the American Society for Parenteral and Enteral Nutrition and the Society of Critical Care Medicine (ASPEN/SCCM), recommend the delivery of 1.2–2.0 g/kg of actual bodyweight per day protein doses, and even greater amounts in patients with burn or multitrauma injuries.[1] These "doses" are two- to three-fold greater than the current mean protein delivered in Australia and New Zealand to critically ill patients (~ 0.6 g/kg)[9] but similar to the amounts recommended by the European Society of Parenteral and Enteral Nutrition and an informal group of global experts.[10,11]

So, should we adhere to recent international guidelines and change practice? Guidelines are intended to ensure that the best evidence is incorporated into practice, but an insufficient appreciation of the quality of evidence may instead lead clinicians to implement treatments that are of no benefit or even harmful.[12,13] Even the authors of the ASPEN/SCCM guidelines recognise that the quality of the evidence supporting increased protein delivery is "very low".[1]

There is a plausible rationale as to why adherence to the guidelines might be of benefit — marked catabolism occurs in the critically ill and loss of muscle mass is associated with morbidity and mortality.[14] In health, dietary protein is a fundamental prerequisite for muscle protein synthesis. Therefore, augmenting protein delivery has the potential to ameliorate the muscle atrophy that occurs during critical illness,[15] which leads to increased mortality in hospital and reduced physical activity in those patients discharged alive,[16,17] such that the wellbeing of survivors may be affected by nutritional interventions.[17-19]

There are also several observational studies that report associations between greater protein administration and the outcomes of interest to health care systems (ie, reduced duration of ventilation and shorter time to discharge alive), as well as patient-centred outcomes (ie, reduced mortality).[20-23] Observations from a well conducted single-centre randomised clinical trial also suggested some benefit in the delivery of the amount of protein recommended in the guidelines.[24]

Nevertheless, there is evidence to contradict the guidelines. Investigators from Leuven have hypothesised that autophagy — the pathway to clear damaged organelles and proteins from muscle and organs — is diminished by protein administration.[25] This hypothesis is supported by observed associations between increased protein delivery and both impaired cellular markers of autophagy and muscle histology in animal models of critical illness, as well as in critically ill adults.[26,27] Moreover, in a pre-planned observational study of 1440 critically ill children within a large randomised clinical trial of parenteral nutrition, increasing the doses of protein was associated with worse outcomes.[28] Finally, in a landmark cohort study conducted in the United Kingdom, investigators observed a relationship between greater loss of quadriceps muscle in critically ill adults and more protein delivered.[29]

Although few randomised clinical trials have specifically addressed optimal protein provision in the critically ill, some trials of nutritional interventions have resulted in differing doses of protein being delivered to each group. Davies and colleagues[30] recently conducted a systematic review and meta-analysis of such randomised clinical trials of nutritional interventions in critically ill patients to evaluate the impact of delivered protein on survival. Twelve studies were extracted, with wide confidence intervals (CIs) around whether provision of more protein reduced or increased mortality (less protein pooled, odds ratio, 0.94; 95% CI, 0.72–1.22). Perhaps of greatest relevance to any proposed change in clinical practice is the fact that there has never been a randomised clinical trial comparing the administration of enteral protein that represents regional standard practice (~ 0.6 g/kg) with what is recommended in international guidelines (> 1.2 g/kg), while controlling for the likely confounding variable of energy delivery.

For these reasons, we suggest that there is insufficient evidence for clinicians to abandon their current practice and adopt the protein goals recommended in recent guidelines. It is possible that increasing protein delivery could improve functional and survival outcomes, but it may also be harmful. We just do not know. However, standard care (ie, enteral protein delivery) is currently 50% of the dose recommended in international guidelines; there is conflicting, although very low level, evidence supporting both current practice and that recommended in international guidelines; and there has never been a randomised clinical trial evaluating standard practice (ie, enteral administered protein) when compared with international guidelines. Moreover, local collaborators working with the ANZICS CTG have established the capacity of our community to conduct programs of work into nutritional therapy which result in the completion of a high-quality phase 3 randomised clinical trial, and its results are likely to be translated into clinical practice. We therefore believe that the Australian and New Zealand community is uniquely placed to conduct a high quality randomised clinical trial to answer the question: "How much protein should I prescribe to this critically ill patient?"

Competing interests

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Author details

Adam M Deane[1,2]
Sandra L Peake[3]
Marianne J Chapman[2,4]

1 Royal Melbourne Hospital, Melbourne, VIC, Australia.
2 Centre for Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, Adelaide, SA, Australia.
3 Department of Intensive Care Medicine, Queen Elizabeth Hospital, Adelaide, SA, Australia.
4 Department of Critical Care Services, Royal Adelaide Hospital, Central Adelaide Health Network, Adelaide, SA, Australia.

Correspondence: adam.deane@mh.org.au

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